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2-Aryl-acetamides as versatile precursors for 3-amino-isocoumarine and homophthalimide derivatives. Pd-catalyzed cascade double carbonylation reactions.

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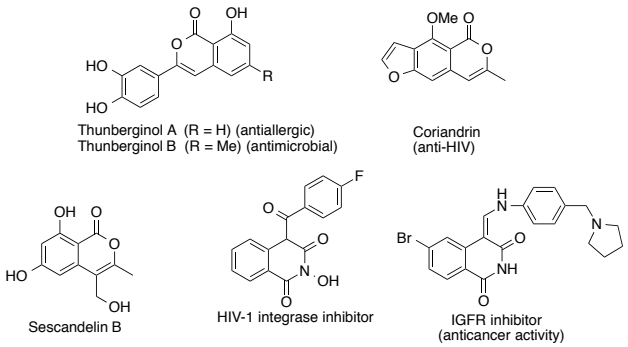
Abstract. The synthesis of biologically relevant homophthalimide and 3-amino-isocoumarine nuclei via palladium-catalyzed carbonylation of 2-(2-iodoaryl)-acetamides has been developed. The degree of *N*-substitution on the starting amide substrate dictates whether a C–N or C–O coupling takes place in the final step of the catalytic cycle giving rise to each type of heterocycle. The introduction of a second C–halogen bond in the starting acetamides allows a catalytic cascade double carbonylation involving a C–H activation step to give fused heterocyclic structures.

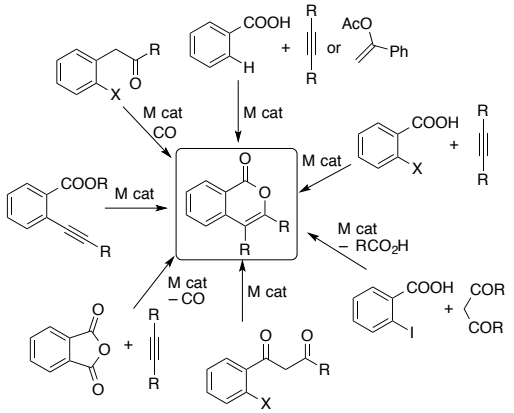
Keywords: Palladium; carbonylation; cascade; heterocycles; C–H functionalization

Isocoumarine and homophthalimide nuclei are privileged six-membered *O*- and *N*-heterocycles, respectively, with a widespread presence in biologically active compounds exhibiting antifungal,[1] anti-inflammatory,[2],[3] and cytotoxic activities,[4],[5] among many others.[6],[7] They are also present in the core of natural products such as sescandelin B or phelligridin D (Scheme 1).



Scheme 1. Examples of biologically active or natural compounds containing the isocoumarine or homophthalimide structural motif.

In the last decades there has been a considerable effort to develop new and efficient synthetic routes to obtain this type of scaffolds with different substitution patterns. The main methods to synthesize isocoumarines involve the cyclization of 1,2-difunctionalized arenes (including ortho-alkynylbenzoic,[8] 2-halobenzoate[9],[10] or phthalic anhydride derivatives[11]) with coupling partners such as alkynes or CO (Scheme 2).[12],[13] Lately, transition-metal catalyzed carboxylate-directed ortho C–H activation of benzoic acid derivatives has emerged as an interesting approach to isocoumarines.[14],[15] All these methodologies give rise to 3,4-alkyl-, aryl-, alkoxy-, acyl- and ester-substituted isocoumarines.



Scheme 2. Main routes for the synthesis of isocoumarines.

The presence of heteroatomic substituents in biologically relevant scaffolds might confer new properties or applications to these compounds. Therefore new synthetic methodologies with the aim of introducing O-,[16] S-,[17] I-,[18]-[20] Br-, Cl-,[19] Se,[18] or Si-[11] substituents in the isocoumarine core are being developed. Only a few papers on the

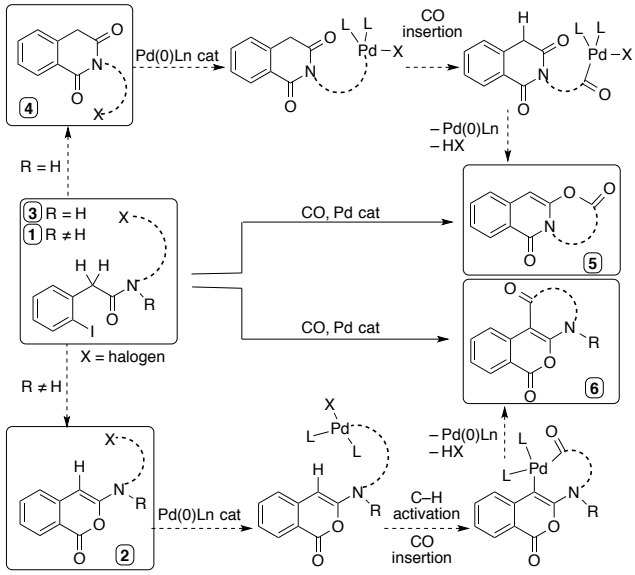
introduction of *N*-substituents in the 3 or 4 positions of the isocoumarine scaffold have been published.[7],[21] Among them, there is a multicomponent Ugi reaction involving the coupling of 2-formylbenzoic acid, an amine and an isocyanide giving rise to 3,4-diamino substituted isocoumarines as the primary adduct.[21]

In contrast to isoquinolones, the synthesis of the structurally related homophthalimides (1,3-isoquinolinediones) has received considerably less attention, in spite of their presence in biologically important compounds. Homophthalimides are mainly obtained by reaction of an amine with homophthalic acid[22] or anhydride derivatives.[2],[23],[24]

The functionalization of 2-arylacetic acids or amides through transition-metal catalyzed C–H activation is an attractive route that has been successfully applied to their arylation,[25],[26] alkenylation,[26] acetoxylation,[27] and halogenation.[28] Nevertheless only a few examples of transition-metal catalyzed carbonylation reactions of these substrates via C–H activation have been reported, requiring harsh conditions (both high temperature and catalyst loading)[29] or the use of a bidentate directing group to facilitate the C–H activation step.[30] Hence, 2-haloaryl-acetamides might be worthy complementary substrates in these carbonylation reactions.

Our research group has been interested in the study of the reactivity of cyclopalladated complexes toward CO.[31] Thus, we reported recently the carbonylation reaction of cyclopalladated arylacetamide complexes.[32] In the stoichiometric model, the nature of the starting amide dictated the outcome of this reaction. When the substrate contained a NH_2 or NHR group, the intermediate acyl-palladium complex underwent a reductive elimination with subsequent C–N bond formation to give the corresponding homophthalimide derivative. Remarkably, when tertiary amides were employed instead, the C–O bond formation took place preferentially upon enolization of the acidic alpha CH_2 group, affording 3-amino-isocoumarines.

Catalytic cascade reactions have gained attention in recent years since they allow the construction of complex molecular structures from simple substrates in a straightforward and efficient manner.[33] In these processes the initial transformation of a conveniently designed substrate affords a new structural motif, which is, in turn, susceptible to undergo a further functionalization carried out by the same catalytic system. Cascade reactions become especially relevant when they involve C–H activation processes in some or all of their steps because they improve the overall atom-economy of the synthesis.[34] We envisioned that the introduction of a pendant reactive site in the nitrogen atom of the starting 2-aryl-acetamide could give rise to structures primed for cascade Pd-catalyzed carbonylation processes (such a those depicted in the Scheme 3) based on the initial production of either homophthalimide or isocoumarine cores.



Scheme 3. Proposed catalytic cascade double carbonylation reactions from 2-arylacetamides.

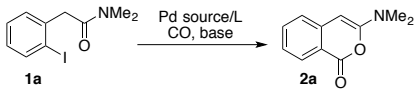
Hence, in this manuscript we report the synthesis of both homophthalimides and 3-amino-isocoumarines from 2-(2-haloaryl)-acetamides in a catalytic fashion, as well as the development of catalytic cascade double carbonylation reactions from the appropriate 2-aryl-acetamide derivatives achieving interesting fused hetrocyclic scaffolds.

We started our study attempting the carbonylation reaction of 2-(2-iodophenyl)-*N,N*-dimethylacetamide (**1a**) using $Pd(dba)_2$ as the Pd(0) source and TMEDA as base/ligand (entry 1, Table 1). These conditions did provide the expected isocoumarine **2a**, albeit in a low yield. After a short optimization process, the yield was improved to nearly full conversion of the starting material by generating Pd(0) *in situ* from simple $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%) in either dry toluene or 1,4–dioxane at 100 °C (entries 3 and 7, Table 1). Lower temperatures or catalyst loadings decreased the performance of the catalytic carbonylation (entries 4, 5 and 6, Table 1). Although the NMR yield for the 3-dimethylamino-isocoumarine **2a** was good, it proved to be sensitive to purification by flash column chromatography on silica-gel, probably due to hydrolysis processes leading to the opening of the heterocyclic structure. The use of neutral alumina improved the efficiency of the chromatographic purification, obtaining a 51% isolated yield of isocoumarine **2a**.

A range of 2-(2-iodophenyl)-*N*,*N*-disubstituted-acetamides **1a**–**g** were submitted to the carbonylation conditions, giving rise to the 3-substituted-isocumarines **2a**–**g** (including cyclic amines as substituents such as piperidine and morpholine) in moderate isolated yields (Scheme 4). The extension of the reaction scope to other heteroatom-containing substrates was performed by using the ester **1h** and

the thioester **1i** as starting materials, which provided the corresponding 3-*O*- and 3-*S*-substituted isocoumarines **2h** and **2i** in moderate yield. The attempts to replace the iodinated substrates **1** for the cheaper but more challenging chlorinated analogues proved unfruitful even heating up to 140 ºC or using the Buchwald's precatalyst as the palladium source.[36]

Table 1. Screening of the reaction conditions for the Pd-catalyzed synthesis of isocoumarine **2a.**[a]



Entry	Pd source (mol%)	ligand (mol%)	base (equiv)	Yield [b]
1	$Pd(dba)_2$ (5)	-	TMEDA (1.2)	10
2	$Pd(dba)_2$ (5)	TMEDA (10)	K_2CO_3 (1)	80
3	$Pd(OAc)_2$ (5)	PPh_3 (20)	K_2CO_3 (1)	95
4	$Pd(OAc)_2$ (2.5)	PPh_3 (10)	K_2CO_3 (1)	90
5	$Pd(OAc)_2$ (1)	PPh_3 (4)	K_2CO_3 (1)	78
6[c]	$Pd(OAc)_2$ (5)	PPh_3 (20)	K_2CO_3 (1)	12
7[d]	$Pd(OAc)_2$ (5)	PPh_3 (20)	K_2CO_3 (1)	96 (51)[e]

[a] Reactions carried out using substrate 1a (0.6 mmol), dry toluene (3 mL) and CO (1.2 atm) in a Carius tube at 100 °C.

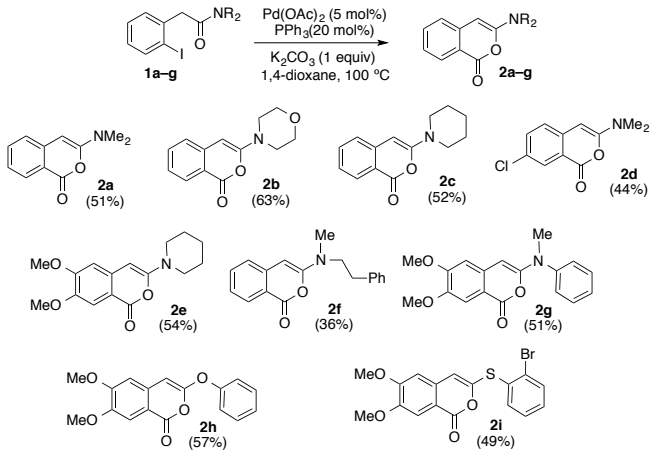
[b] NMR yields.

[c] Reaction carried out at 50 °C.

[d] Dry 1,4–dioxane (3 mL) was used as the solvent.

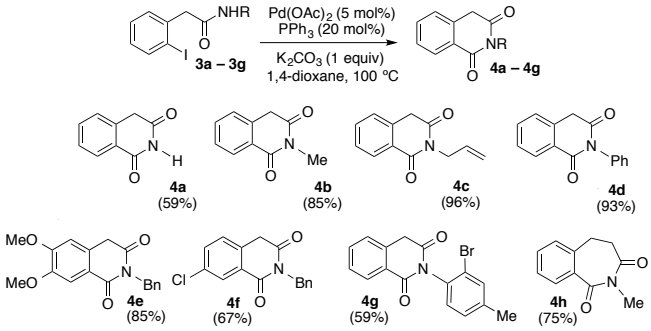
[e] Isolated yield after column chromatography.

[f] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



Scheme 4. Scope on 3-*N*-, *O*- and *S*-substituted isocoumarines.

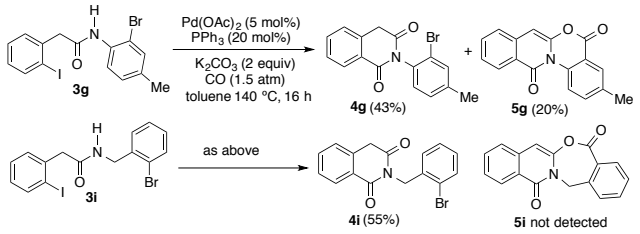
We then turned our attention to unsubstituted or *N*-monosubstituted 2-aryl-acetamide substrates **3a**–**3g**. As stated in our previous stoichiometric study,[32] the palladium-catalyzed carbonylation of these substrates led to the formation of homophthalimides **4a**–**4g** in good yields (Scheme 5). The reaction tolerates well alkyl-, allyl- and aryl-substituents on the nitrogen atom, as well as the presence of electron-donating or electron-withdrawing groups in the aromatic ring. The presence of a bromine atom in the *N*-aryl substrate **3g** was tolerated under the reaction conditions, obtaining a 59% yield of the homophthalimide **4g**. The method could be extended to the synthesis of the 7-membered benzazepin-1,3-dione **4h** in good yield by using *N*-methyl-3-(2-iodophenyl)-propanamide as starting material.[35]



Scheme 5. Scope of the synthesis of homophthalimide.

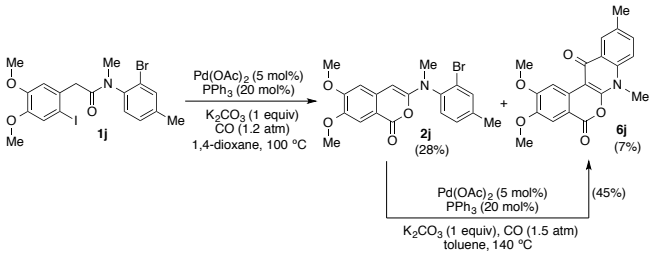
With these reaction conditions in hand, we decided to explore the use of 2-(2-iodoaryl)-acetamides for the development of catalytic cascade carbonylation processes. We reasoned that the cascade cyclization leading to the fused heterocyclic systems **5** and **6** (Scheme 3) could be successful when the tethering chain on the nitrogen atom fulfilled two conditions: first, it should contain a reactive site which should not hamper the initial oxidative addition of the C–I bond to Pd(0) (in order to render the desired homophthalimide/isocoumarine intermediate); and second, the length of the tethering chain should be appropriated to place the Pd atom in close proximity to the homophthalimide or isocoumarine core, allowing the cyclization step to occur. We chose the 2-bromoaryl moiety as a suitable substituent on the nitrogen atom of the amide. The C–I bond present in the aryl substrates undergoes a faster oxidative addition to Pd(0) compared to the C–Br bond, hence the later would not represent a significant competitor in the first step of the reaction, minoring the generation of by-products. Moreover, the oxidative addition of palladium to the C–Br bond of the resulting *N*-aryl substituted isocoumarines **2** or homophthalimides **4** (Scheme 3), would lead to suitable six-membered palladacycles where CO insertion and oxidative cyclization is possible, as demonstrated in stoichiometric models of similar size.[31a,d], [32].

We had observed that the *N*-aryl substituted acetamide **3g** (bearing the bromine atom) afforded the homophthalimide **4g** in good yield. Hence we attempted harsher conditions in order to make it further react. The desired fused heterocycle **5g** was indeed formed when the reaction was performed in dry toluene at 140 °C, albeit in a low 20 % yield (Scheme 6). Unfortunately, the change of other reaction parameters such as the base (*t*-BuOK), catalyst loading (increased to 10%), reaction times (up to 24 h) or the palladium(0) source (Buchwald's precatalyst)[36] did not improve the formation of **5g**. The double carbonylation was also unsuccessful with the substrate **3i** bearing a 2-bromobenzyl substituent on the nitrogen atom (Scheme 6).



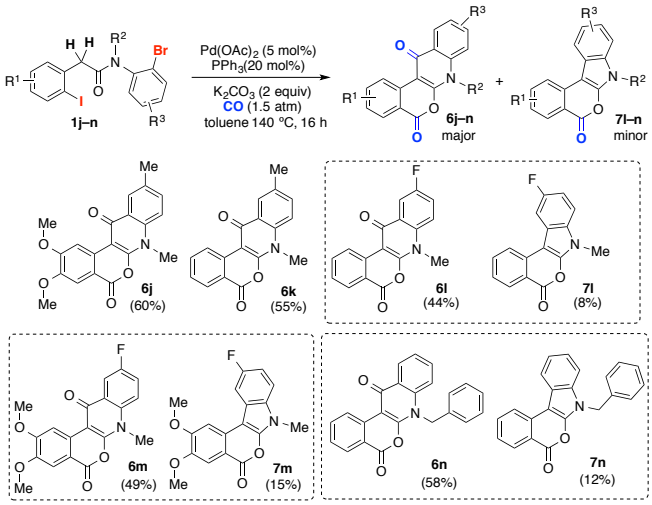
Scheme 6. Attempted catalytic double carbonylation of homophthalimide derivatives.

Next, we focused on the cascade reaction based on the initial formation of the isocoumarine core. When the *N*-arylated acetamide **1j** was submitted to the standard catalytic carbonylation conditions (1,4-dioxane at 100 °C) a small amount of the expected fused heterocycle **6j** was formed, along with a substantial amount of the isocoumarine derivative **2j** (Scheme 7).



Scheme 7. Synthesis of the fused heterocycle **6j** from **1j** and **2j**.

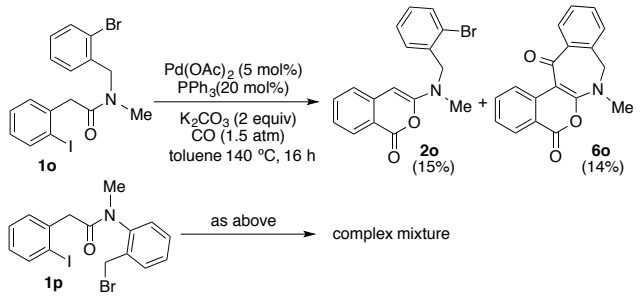
We were pleased to observe the increase in the yield of the doubly carbonylated product **6j** to 60 % when the reaction was performed in toluene at 140 °C (Scheme 8). The replacement of PPh_3 for other bidentated phosphine ligands such as dppe or dppf gave divergent results. While dppe hampered the second carbonylation, affording only traces of **6j** and a 12% of the indol derivative **7j**, dppf gave nearly the same results as those obtained with PPh_3, 62 % of the doubly carbonylated product **6j** and a small amount of **7j**. The cascade carbonylation could be extended to the substrates **1j**–**n**, which afforded the corresponding heterocycles **6j**–**6n** in moderate isolated yields, showing the tolerance of the reaction to both electron-donating and electron-withdrawing groups in the starting materials (Scheme 8). The required tertiary nature of the amides **1j**–**n** (for the reaction to proceed through the isocoumarine formation) could be accomplished with groups such as Me or Bn on the nitrogen atom. Along with the formation of compounds **6**, the reaction produced a concomitant small amount of the indole derivatives **7**, which could be isolated and characterized in the cases of the substrates **2l**–**n**. Noteworthy, the overall cascade double carbonylation reaction represents the breakage of two C–halogen and two C–H bonds in the substrates **1** giving rise to the formation of one C–O and three C–C new bonds present in the scaffolds **6**.



Scheme 8. Catalytic cascade carbonylation of subtrates **1j**–**n**.

We also explored more challenging substrates which could potentially lead to seven-membered rings when submitted to the cascade carbonylation reaction. While the substrate **1o** afforded the expected polycyclic product **6o** in low yield (14%) along with the intermediate 3-amino-isocoumarine **2o**, the substrate **1p**, bearing a benzylic bromide moiety, gave a complex mixture of products (Scheme 9).

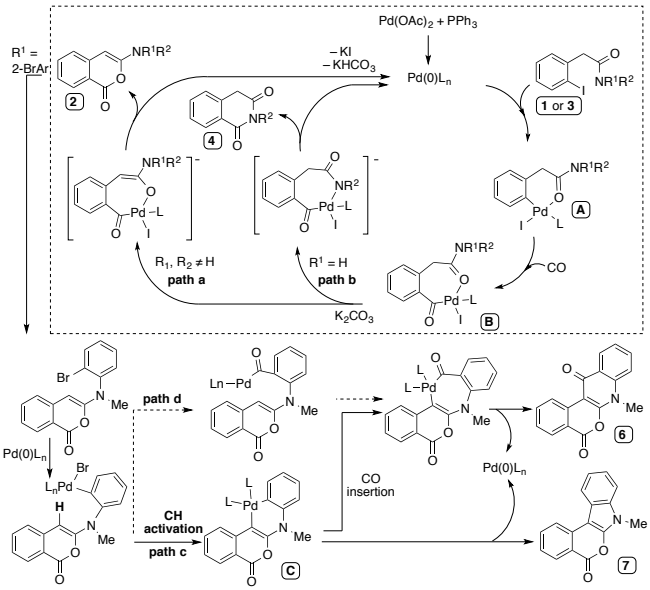
In order to confirm that isocoumarines **2** are the intermediates in the synthesis of the doubly carbonylated products **6**, the isocoumarine **2j** was submitted to the standard cascade carbonylation conditions with $Pd(OAc)_2/PPh_3$ in toluene at 140 °C for 12 h, affording a 45% yield of **6j** (Scheme 7). These results, along with the isolation of the indole derivatives **7j**–**n** in the reactions with substrates **2j**–**n**, strongly point toward a C–H activation step involving the alkenyl group present in the isocoumarines **2**.



Scheme 9. Carbonylation reaction of substrates leading to seven-memberd rings.

Palladium-mediated or catalyzed carbonylation reactions have become a powerful and versatile tool to introduce one carbonyl group in organic substrates.[37] Nevertheless, double carbonylation processes remain underexplored and are mainly restricted to a reduced number of transformations, being the synthesis of α-diketo derivatives the most developed.[38] Remarkably, double carbonylation reactions involving C–H activation steps are exceptionally rare.[39]

Most likely, the reaction pathways followed by the two types of 2-aryl-acetamides **1** (tertiary amides) and **3** (primary/secondary amides) in the carbonylation process share some common intermediates, which are depicted in Scheme 10. The oxidative addition to *in situ* generated Pd(0) species of the C–I bond present in the starting material would generate a six-membered intermediate palladacycle **A**, which could undergo the insertion of CO into the Pd–C bond leading to a Pd–acyl intermediate **B**. The participation of intermediates **A** and **B** in the reaction was confirmed by previous stoichiometric studies, where such compounds where isolated.[32] The decomposition pathway of the intermediate **B** depends on the degree of substitution on the nitrogen atom. When the starting amide is tertiary, the formation of the C–N bond is disfavoured. Instead, the presence of acidic protons in alpha position to the amide moiety enables the formation of an enolate intermediate which evolves through an oxidative C–O bond formation, leading to 3-amino-isocoumarines **2** (path a, Scheme 10). In the case of primary and secondary 2-aryl-acetamides, the C–N bond formation is preferred, giving rise to homophthalimide derivatives **4** (path b, Scheme 10). The substrates **1j**–**n** (bearing the 2-bromoaryl substituent on the nitrogen atom) could undergo a further oxidative addition to Pd(0), placing the resulting Pd(II) atom in a privileged position to activate the alkenyl C–H bond of the isocoumarine core (path c, Scheme 10) to afford the six-membered C,C-palladacycle **C**. This intermediate could undergo the reductive elimination of Pd(0) with subsequent formation of the indole derivatives **7**. Nevertheless, CO insertion into any of the C–Pd bonds of palladacycle **C** may happen preferentially prior to the reductive elimination step, producing the fused heterocycles **6**. Alternatively, the CO insertion step could also take place before the C–H activation event (path d, Scheme 10). The formation of the indole derivatives **7** might possibly be minored in favour of the heterocycles **6** under high CO pressure conditions. An additional reaction pathway involving a Heck-type palladation of the alkenyl moiety of the *N*-2-bromoaryl isocoumarines **2** by Pd(II) species can not completely be ruled out, however it seems less probable since it would imply the further oxidative addition of the C–Br bond to give a Pd(IV) intermediate, which could later undergo the CO insertion.



Scheme 10. Possible reaction pathway for the synthesis of 3-amino-isocoumarines **2**, homophthalimides **4** and the doubly carbonylated products **6**.

In summary, we have developed the palladium-catalyzed carbonylation reaction of 2-(2-iodoaryl)-acetamides, extensible to esters and thioesters. This synthetic methodology enables the use of CO as a cheap C1 feedstock in the synthesis of homophthalimides and 3-amino-isocoumarines, depending on whether the starting material is a primary/secondary or tertiary arylacetamide. These carbonylation reactions constitute a new way to introduce *N*-, O- and *S*-substituents in the isocoumarine scaffold. Moreover, conveniently designed arylacetamides allow the performance of cascade double carbonylation involving the activation of the alkenyl C–H moiety present in the 3-substituted isocoumarine core, affording interesting fused heterocycles.

Experimental Section

Representative procedure for the synthesis of isocoumarine and homophthalimide derivatives 2 and 4.

A Carius tube was charged with the starting acetamide (**1** or **3**) (0.6 mmol, 1 equiv), K_2CO_3 (83 mg, 0.6 mmol, 1

equiv), $Pd(OAc)_2$ (7 mg, 0.03 mmol, 5 mol%), PPh_3 (32 mg, 0.122 mmol, 20 mol%) and a teflon-coated stirrer bar. Three vacuum-nitrogen cycles were applied to the tube and dry 1,4-dioxane (3 mL) was added. The tube was evacuated, refilled with CO (1.2 atm) and sealed. The reaction mixture was heated in an oil-bath at 100 °C for 16 h. After cooling the Carius tube to rt, the reaction mixture was diluted with EtOAc (30 mL) and filtered through a Celite pad. The filtrate was concentrated and the crude product was purified by column chromatography.

Representative procedure for the synthesis of derivatives 6.

A Carius tube was charged with *N*-arylacetamide (**1**) (0.5 mmol, 1 equiv), K_2CO_3 (140 mg, 1 mmol, 2 equiv), $Pd(OAc)_2$ (6 mg, 0.026 mmol, 5 mol%), PPh_3 (26 mg, 0.099 mmol, 20 mol%) and a teflon-coated stirrer bar. Three vacuum-nitrogen cycles were applied to the tube and dry toluene (3 mL) was added. The tube was evacuated, refilled with CO (1.5 atm) and sealed. The reaction mixture was heated in an oil-bath at 140 °C for 16 h. After cooling the Carius tube to rt, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and filtered through a Celite pad. The filtrate was concentrated to ca. 2 mL and the crude was purified either by column chromatography or fractional crystallization.

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References

[1] K. Nozawa, M. Yamada, Y. Tsuda, K.-I. Kawai, S. Nakajima, *Chem. Pharm. Bull.* **1981**, *29*, 2689.

[2] E. S. Lazer, R. Sorcek, C. L. Cywin, D. Thome, G. J. Possanza, A. G. Graham, L. Churchill, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1181.

[3] H. Matsuda, H. Shimoda, J. Yamahara, M. Yoshikawa, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215.

[4] A. C. Whyte, J. B. Gloer, *J. Nat. Prod.* **1996**, *59*, 765.

[5] S. C. Mayer, A. L. Banker, F. Boschelli, L. Di, M. Johnson, C. H. Kenny, G. Krishnamurthy, K. Kutterer, F. Moy, S. Petusky, M. Ravi, D. Tkach, H.-R. Tsouc, W. Xu, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3641.

[6] a) M. Billamboz, V. Suchaud, F. Bailly, C. Lion, J. Demeulemeester, C. Calmels, M.-L. Andréola, F. Christ, Z. Debyser, P.Cotelle, *ACS Med. Chem. Lett.* **2013**, *4*, 606−611; b) Y. -L. Chen, J. Tang, M. J. Kesler, Y. Y. Sham, R. Vince, R. J. Geraghty, Z. Wang, *Bioorg. Med. Chem. Lett.* **2012**, *20*, 467; c) G. A. Kraus, J. Ridgeway, *J. Org. Chem.* **1994**, *59*, 4735; d) M. Chinworrungsee, P. Kittakoop, M. Isaka, R. Chanphen, M. Tanticharoen, Y. Thebtaranonth, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2473; e) C.-M. Kam, K. Fujikawa, J. C. Powers, *Biochemistry* **1998**, *27*, 2547; f) V. Suchaud, F. Bailly, C. Lion, C. Calmels, M. -L. Andréola, F. Christ, Z. Debyser, P. Cotelle, *J. Med. Chem.* **2014**, *57*, 4640.

[7] S. L. Payne, S. Rodriguez-Aristegui, J. Bardos, C. Cano, B. T. Golding, I. R. Hardcastle, M. Peacock, N. Parveen, R. Griffin, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3649.

[8] a) H. Wang, X. Han, X. Lu, *Tetrahedron* **2013**, *69*, 8626; b) M. Al-Amin, J. S. Johnson, S. A. Blum, *Organometallics* **2014**, *33*, 5448; c) M. Biagetti, F. Bellina, A. Carpita, P. Stabile, R. Rossi, *Tetrahedron* **2002**, *58*, 5023.

[9] a) M. A. Waseem, Shireen, A. A. Abumahdi, A. Srivastava, A. Srivastava, Rahila, I. R. Siddiqui, *Catal. Commun.* **2014**, *55*, 70; b) R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem* **1999**, *64*, 8770.

[10] W. J. Ang, C.-H. Tai, L.-C. Lo, Y. Lam, *RSC Adv.* **2014**, *4*, 4921.

[11] a) Y. Kajita, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2008**, *130*, 17226; b) R. Prakash, K. Shekarrao, S. Gogoi, R. C. Boruah, *Chem. Commun.* **2015**, *51*, 9972; c) H. Xie, Q. Sun, G. Ren, Z. Cao, *J. Org. Chem.* **2014**, *79*, 11911.

[12] For carbonylation of 2-(2-haloaryl)ketones see: a) I. Shimoyamal, Y. Zhang, G. Wu, E. Negishi, *Tetrahedron Lett.* **1990**, *31*, 2841; b) E. Negishi, C. Coperet, T. Sugiham, I. Shimoyama, Y. Zhang, G. Wu, J. M. Tour, *Tetrahedron* **1994**, *50*, 425; c) E. Negishi, H. Makabe, I. Shirnoyamag, G. Wu, Y. Zhang, *Tetrahedron* **1998**, *54*, 1095; d) A. C. Tadd, M. R. Fieldingb, M. C. Willis, *Chem. Commun.* **2009**, 6744.

[13] a) D. E. Korte, L. S. Hegedus, R. K. Wirth, *J. Org. Chem.* **1977**, *42*, 1329; b) K. Cherry, J.-L. Parrain, J. Thibonnet, A. Duchêne, M. Abarbr, *J. Org. Chem.* **2005**, *70*, 6669; c) M. Chakravarty, K. C. K. Swamy, *J. Org. Chem* **2006**, *71*, 9128; d) S. Cai, F. Wang, C. Xi, *J. Org. Chem.* **2012**, *77*, 2331; e) Z.-Y. Ge, X.-D. Fei, T. Tang, Y. -M. Zhu, Shen, J.-K. *J. Org. Chem.* **2012**, *77*, 5736; f) X.-D. Fei, Z.-Y. Ge, T. Tang, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem.* **2012**, *77*, 10321; g) P.-Y. Chen, K.-S. Huang, C.-C. Tsai, T.-P. Wang, E.-C. Wang, *Org. Lett.* **2012**, *14*, 4930; h) S. K. Gadakh, A. Sudalai, *RSC Adv.* **2014**, *4*, 57658; i) S. Özcan, E. Sahin, M. Balci, *Tetrahedron Lett.* **2007**, *48*, 2151; j) S. Özcan, M. Balci, *Tetrahedron* **2008**, *64*, 5531.

[14] a) D. A. Frasco, C. P. Lilly, P. D. Boyle, E. A. Ison, *ACS Catal.* **2013**, *3*, 2421; b)R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030; c) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 ; d) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem* **2007**, *72*, 5362; e) M. Shimizu, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 3478; f) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; g) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930.

[15] M. Zhang, H.-J. Zhang, T. Han, W. Ruan, T.-B. Wen, *J. Org. Chem.* **2015**, *80*, 620.

[16] a) B. Chen, S. Ma, *Org. Lett.* **2013**, *15*, 3884; b) F. Bihel, G. Quéléver, L. Hugues, A. Petit, C. A. Costa, O. Pourquié, F. Checler, A. Thellend, P. Pierree, J.-L. Krausa, *Bioorg. Med. Chem. Lett.* **2003**, *11*, 3141; c) J.

E. Kerrigan, J. Oleksyszyn, C.-M. Kam, J. Selzler, J. C. Powers, *J. Med. Chem.* **1995**, *38*, 544.

[17] Y. Li, G. Li, Q. Ding, *Eur. J. Org. Chem.* **2014**, 5017.

[18] T. Yao, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 5936.

[19] M. Peuchmaur, V. Lisowski, C. Gandreuil, L. T. Maillard, J. Martínez, J.-F. Hernández, *J. Org. Chem.* **2009**, *74*, 4158.

[20] A. K. Verma, V. Rustagi, T. Aggarwal, A. P. Singh, *J. Org. Chem.* **2010**, *75*, 7691.

[21] a) C. Faggi, M. García-Valverde, M. Stefano, G. Menchi, *Org. Lett.* **2010**, *12*, 788; b) A. Ramazani, A. Mahyari, *Helv. Chim. Acta* **2010**, *93*, 2203; c) D. R. J. Acke, C. V. Stevens, *Green Chem.* **2007**, *9*, 386; d) T. Opatz, D. Ferenc, *Eur. J. Org. Chem.* **2005**, 817.

[22] Homophtalic acids are prepared in turn through a) oxidative cleavage of indene derivatives, see: S. K. V. Vernekar, Z. Liu, E. Nagy, L. Miller, K. A. Kirby, D. J. Wilson, J. Kankanala, S. G. Sarafianos, M. A. Parniak, Z. Wang, *J. Med. Chem.* **2015**, *58*, 651.b) lateral lithiation followed by carboxylation of *ortho*-toluic acid, see: H.-R. Tsou, M. Otteng, T. Tran, M. J. Brawner Floyd, M. Reich, G. Birnberg, K. Kutterer, S. Ayral-Kaloustian, M. Ravi, R. Nilakantan, M. Grillo, J. P. McGinnis, S. K. Rabindran, *J. Med. Chem.* **2008**, *51*, 3507 or c) copper catalyzed coupling of 2-halobenzoic acid and acetoacetate esters, see: S. D. Young, J. M. Wiggins, J. R. Huff, *J. Org. Chem.* **1988**, *53*, 1114; M. S. Malamas, T. C. Hohman, J. Millent, *J. Med. Chem.* **1994**, *37*, 2043.

[23] a) W. J. Gender, S. F. Lawless, A. L. Bluhm, H. Dertouzos, *J. Org. Chem.* **1975**, *40*, 733; b) R. J. Snow, M. G. Cardozo, T. M. Morwick, C. A. Busacca, Y. Dong, R. J. Eckner, S. Jacober, S. Jakes, S. Kapadia, S. Lukas, M. Panzenbeck, G. W. Peet, J. D. Peterson, A. S. Prokopowicz, R. Sellati, R. M. Tolbert, M. A. Tschantz, N. Moss, *J. Med. Chem.* **2002**, *45*, 3394.

[24] For alternative synthesis see: a) L. Li, Y.-L. Zhao, H. Wang, Y.-J. Li, X. Xu, Q. Liu, *Chem. Commun.* **2014**, *50*, 6458; b) W. Kong, M. Casimiro, N. Fuentes, E. Merino, C. Nevado, *Angew. Chem.* **2013**, *125*, 13324; *Angew. Chem. Int. Ed.* **2013**, *52*, 13086; c) Y. Pan, C. P. Holmes, D. Tumelty, *J. Org. Chem.* **2005**, *70*, 4897; d) B. Quiclet-Sire, S. Z. Zard, *Chem. Commun.* **2002**, 2306.

[25] (a) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676; b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331; Y. Wang, K. Zhou, Q. Lan, X.-S. Wang, *Org. Biomol. Chem.* **2015**, *13*, 353.

[26] N. Dastbaravardeh, T. Toba, M. E. Farmer, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 9877.

[27] R. K. Rit, M. R. Yadav, A. K. Sahoo, *Org. Lett.* **2014**, *16*, 968.

[28] T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140.

[29] R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14082.

[30] a) K. Shibata, N. Hasegawa, Y. Fukumoto, P. N. Chatani, *Chem. Cat. Chem.* **2012**, *11*, 1733; b) N. Hasegawa, K.Shibata, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *Tetrahedron* **2013**, *69*, 4466.

[31] a) J.-A. García-López, M. -J. Oliva-Madrid, I. Saura-Llamas, D. Bautista, J. Vicente, *Organometallics* **2012**, *31*, 6351; b) J.-A. García-López, M.-J. Oliva-Madrid, I. Saura-Llamas, D. Bautista, J. Vicente, *Organometallics* **2013**, *32*, 1094; c) M.-J. Oliva-Madrid, J.-A. García-López, I. Saura-Llamas, D. Bautista, J. Vicente, *Organometallics* **2014**, *33*, 19.

[32] J. Vicente, P. González-Herrero, R. Frutos-Pedreño, M.-T. Chicote, P. G. Jones, *Organometallics* **2011**, *30*, 1079.

[33] a) C.-N. Feng, Y.-C. Hsieh, Y.-T. Wu, *Chem. Rec.* **2015**, *15*, 266; b) X. Just-Baringo, D. J. Procter, *Acc. Chem. Res.* **2015**, *48*, 1263; c) *Barry B. Toure, Dennis G. Hall, Chem. Rev*. **2009**, *109*, 4439; d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, 118, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

[34] a) W. Yang, S. Ye, D. Fanning, T. Coon, Y. Schmidt, P. Krenitsky, D. Stamos, J.-Q. Yu, *Angew. Chem.* **2015** , *127*, 2531; *Angew. Chem. Int. Ed*. **2015**, *47*, 2501; b) S. K. Bhunia, A. Polley, R. Natarajan, R. Jana, *Chem. Eur. J.* **2015**, *21*, 16786; c) Burns, D. J.; Best, D.; Wieczysty, M. D.; Lam, H. W. *Angew. Chem.* **2015** , *127*, 10096; *Angew. Chem., Int. Ed.* **2015**, *54*, 9958; d) V. P. Mehta, J. A. Garcia-Lopez, M. F. Greaney, *Angew. Chem*. **2014**, *126*, 1555; *Angew. Chem. Int. Ed*. **2014**, *53*, 1529; e) D. Zhao, F. Lied, F. Glorius, *Chem. Sci.* **2014**, 5, 2869–2873. f) J. Zhao, K. Oniwa, N. Asao, Y. Yamamoto, T. Jin, *J. Am. Chem. Soc*. **2013**, *135*, 10222; g) S. Duttwyler, C. Lu, A. L. Rheingold, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 4064; h) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem.* **2008**, *120*, 4083; *Angew. Chem. Int. Ed*. **2008**, 47, 4019–4022.

[35] R. Frutos-Pedreño, P. González-Herrero, J. Vicente, P. G. Jones, *Organometallics* **2013**, *32*, 1892.

[36] A 5 mol% of orthopalladated phenethylamine complex bearing the Sphos ligand was used. This precatalyst was prepared according to the procedure described in J. Vicente, I. Saura-Llamas, M.-J. Oliva-Madrid, J.-A. García-López, *Organometallics*, **2011**, *30*, 4624.

[37] a) C. Shen, W. Li, H. Yin, A. Spannenberg, T. Skrydstrup, X.-F. Wu, *Adv. Synth. Catal.* **2016**, *358*, 466. b) J. Chen, K. Natte, H. Neumann, X.-F. Wu, *Chem. Eur. J.* **2014**, *20*, 16107. c) A. McNally, B.Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature*, **2014**, *510*, 129; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1; e) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515; f) B. López, A. Rodriguez, D. Santos, J. Albert, X. Ariza, J. García, J. Granell, *Chem. Commun.* **2011**, *47*, 1054; g) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M.

Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342.

[38] a) C. Shen, N. Y. T. Man, S. Stewartb, X.-F. Wu, *Org. Biomol. Chem*. **2015**, *13*, 4422. b) K. Natte, J. Chen, H. Li, H. Neumann, M. Beller, X.-F. Wu, *Chem. Eur. J.* **2014**, 20, 14184; c) S. Gao, M. Chen, M-N. Zhao, W. Du, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *J. Org. Chem.* **2014**, 79, 4196; d) J. Chen, K. Natte, A. Spannenberg, H. Neumann, M. Beller, X.-F. Wu. *Org. Biomol. Chem.,* **2014**, 12, 5578; e) S. T. Gadge, B. M. Bhanage, *J. Org. Chem.* **2013**, 78, 6793; f) J. Schranck, X.-F. Wu, A. Tlili, H. Neumann, M. Beller. *Chem. Eur. J.* **2013**, 19, 12959; g) M. V. Khedkar, S. R. Khan, D. N. Sawant, D. B. Bagal, B. M. Bhanage. *Adv. Synth. Catal.* **2011**, 353, 3415; h) X.-F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, 17, 12246; i) H. Cao, W.-J. Xiao, H. Alper, *Adv. Synth. Catal.* **2006**, *348*, 1807; j) Y.-S. Lin, H. Alper*, Angew. Chem.* **2001**, *113*, 801; *Angew. Chem. Int. Ed.* **2001**, 40, 779; k) S. Murahashi, Y. Mitsue, K. Ike. *J. Chem. Soc. Chem. Commun.* **1987**, 125-127; l) M. Tanaka, T. Kobayashi, T. Sakakura, *J. Chem. Soc. Chem. Commun.* **1985**, 837-838; m) F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto, A. Yamamoto, *J. Am. Chem. Soc.* **1985**, 107, 3235.

[39] W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, *Angew. Chem.* **2015**, *127*, 1913; *Angew. Chem. Int. Ed.* **2015**, 54, 1893.

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