Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202202350
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Direct Synthesis of 3-Aryl Substituted Isocoumarins and Phthalides through Palladium Acetate Catalyzed C(sp^2)–H Activation in Ionic Liquids

Andrea Aloia,[a] Michele Casiello,[a] Lucia D'Accolti,[a, b] Caterina Fusco,[b] Angelo Nacci,[a, b] and Antonio Monopoli*[a, b]

Abstract: A novel Pd-catalysed oxidative coupling between benzoic acids and vinylarenes or acrylates to furnish isocoumarins and phthalides is reported. The reaction proceeds smoothly in molten tetrabutylammonium acetate via a selective C–H bond activation, with very low percentage of ligand-free palladium acetate as the catalyst, under atmospheric pressure of oxygen. Sub-stoichiometric amount of copper acetate is also required as a reoxidant for the palladium.

Introduction

Isocoumarins and 3,4-dihydroxycoumarins are an important class of molecules that play a crucial role in pharmacology and medicine, with biological properties ranging from anti-HIV,[1] diuretic and antihypertensive activity[2] to the treatment of lymphatic system disease.[3,4] Furthermore, phyllodulcin,[5] a 3,4-dihydroxicoumarin derived from flowers of *hydrangea serrata* and *hydrangea macrophylla*, is a powerful sweetener used for nearly a thousand years in *amatcha* tea in Japan. Moreover, they can also exhibit a strong toxicity as the skeleton of isocoumarin is present in ochratoxin compounds, natural molecules possessing neurotoxic, teratogenic, genotoxic, or immunotoxic properties.[6]

Due to their importance, several synthetic methods have been described until now, which can be mainly grouped into the two categories of metal-free and metal-catalyzed reactions.[7] Among them, other subdivisions can be made, depending on the nature of the substrate. In fact, some protocols start from 2-alkynylbenzoic (or benzoate) acids, leading to the target molecules via an intramolecular metal free cyclization[6,8] or by silver, copper, or palladium-catalysed reactions; other procedures refer to the coupling of 2-halo-/triflate benzoic acids (or other halo-derivatives) with enolates or alkynes,[9,10] while recent papers perform the synthesis of isocoumarins via C–H functionalization of benzoic acids without decarboxylation.

In this kind of reactions annulation is commonly achieved by using a substituted alkyne in order to maintain a double bond in the heterocycle. Alternatively, very few papers deal with the synthesis of isocoumarins starting from benzoic acids coupled with alkenes.

In 1984, Larock et al., obtained isocoumarins by orthothallation of benzoic acids and subsequent reaction with stoichiometric amounts of palladium chloride and simple alkyl olefins.[11] Almost 15 years later, Miura and co-workers succeeded in the synthesis of methylphthalide and 3-phenylisocoumarin, by reacting substituted benzoic acids with acrylates or styrene. Reactions were conducted in DMF, under air, with 10 mol% of palladium acetate as the catalyst and comparable amounts of copper acetate as the reoxidant.[12] In addition, the use of molecular sieves was also mandatory.

Later, functionalization of the ortho C–H bond of the benzoic acid was also achieved by Lee et al. under similar conditions (5 mol% of Pd in DMF), but using stoichiometric amounts of Ag(I) in place of copper as the reoxidant.[13]

Inspired by our studies on the use of ionic liquids (ILs) in organic synthesis,[14–17] we predicted that these alternative non-innocent solvents, relatively unexplored in this type of couplings, could lead to a net improvement of both yields and selectivities. We report herein a straightforward strategy to obtain 3-substituted isocoumarins and phthalides by an easy C–H bond alkenylation of benzoic acids promoted by $Pd(OAc)_2$ in molten tetrabutyl ammonium acetate (TBAA) as the reaction medium.

[a] *Dr. A. Aloia, Dr. M. Casiello, Prof. L. D'Accolti, Prof. A. Nacci, Dr. A. Monopoli*
Chemistry Department
Università degli Studi di Bari Aldo Moro
Via Orabona 4, 70126 Bari (Italy)
E-mail: antonio.monopoli@uniba.it

[b] *Prof. L. D'Accolti, Dr. C. Fusco, Prof. A. Nacci, Dr. A. Monopoli*
CNR – Istituto di Chimica dei Composti Organometallici (ICCOM)
Bari Section
Consiglio Nazionale delle Ricerche
Via Orabona 4, 70126 Bari (Italy)

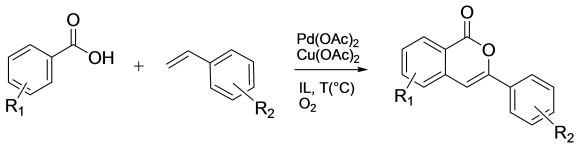
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202202350

Results and Discussion

Recently, some of us succeeded in performing an unusual cyclopropanation reaction between methyl ketones and styrenes via a dehydrogenative cyclizing process involving the α-position of the ketone. The coupling occurred via a twofold C–H activation promoted by $Pd(OAc)_2$ and $Cu(OAc)_2$ in a molten quaternary ammonium salt as the reaction medium. The nature of the IL counterion was found to be crucial and the formation of a pivotal oxa-π-allyl palladium complex intermediate was suggested and confirmed by ESI-HRMS analyses.[18]

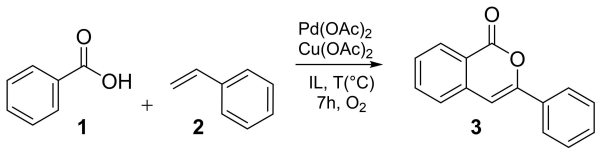
Since transition metal-promoted ortho-CH aromatic activation driven by the presence of a carboxylic group is a quite similar process, we speculated that the coupling between benzoic acids and styrenes leading to isocoumarins, should occur very smoothly by adopting our previous cyclopropanation conditions (Scheme 1).

With this in mind, we started investigations searching for the best IL for this process. The solvent scope was surveyed on the coupling between benzoic acid **1** and styrene **2** as model substrates (Table 1). At first, for comparison, a molecular solvent such as DMA was tested, which showed poor performances with the small catalyst concentrations of 1–3 mol% adopted (Table 1, runs 1–2). These results are in line with the literature where a minimum amount of 5 mol% of Pd salt (up to 10%) was found to be necessary for carrying the coupling.[11–13]



Scheme 1. Palladium catalyzed synthesis of isocoumarins.

Table 1. Solvent scope.[a]



1 + **2** → **3**

Run	$Pd(OAc)_2$ [mol%]	**1**/**2** ratio	Solvent	T [°C]	Yield of **3**[b] [%]
1	1.5	2:1	DMA	110	7
2	3	2:1	DMA	110	13
3	1.5	2:1	BMIMBr	110	<5
4	1.5	2:1	BMIMOAc	110	<5
5	1.5	2:1	$BMIMBF_4$	110	<5
6	1.5	2:1	TBAB	110	<5
7	1.5	2:1	TBAB	110	42[c]
8	1.5	2:1	$TBAOH/H_2O$	100	23
9	0.5	2:1	$TBAOH/H_2O$	100	8
10	1.5	2:1	TBAA	110	35 (75)[d]
11	0.5	2:1	TBAA	110	84 (73)[e]
12	0.5	2:1	TBAA	90	55 (84)[f]
13	0.5	1:1	TBAA	110	64[g]

[a] Reaction conditions: benzoic acid 5 mmol, styrene 2.5 mmol, DMF: 1 mL or IL: 0.5 g, $Cu(OAc)_2$: 1 equiv., for 7 h. [b] Yield based on GC-MS analysis with external standard. [c] 20% of TBAA was added. [d] After 22 h. [e] Isolated yield. [f] Chromatographic yield after 24 h. [g] 15% of 1,4-diphenyl-1,4-butadiene was also detected.

Similar disappointing results were found with imidazolium-based ionic liquids (Table 1, runs 3–5), whereas in quaternary ammonium salts, yields in isocoumarin were found to be dependent on the nature of counter anion, ranging from very low to high (Table 1, runs 6–13).

In particular, in tetrabutylammonium bromide (TBAB), reaction proceeded with scarce results (<5%, run 6), but the addition of 20 mol% of tetrabutylammonium acetate (TBAA) increased yield to 42% (run 7), thus indicating the beneficial effect of a basic anion.

However, the use of IL bearing a strong base such as hydroxide anion didn't afford any improvement (Table 1, run 8,9). On the contrary, the use of tetrabutylammonium acetate as the sole reaction medium enabled a smooth coupling, affording 3-phenyl-1H-isochromen-1-one **3** in good yield (Table 1, runs 10–13).

Notably, the beneficial effect of ionic liquid medium allowed a further lowering of palladium concentration to 0.5 mol% with the simultaneous increase of yield to 84% (Table 1, run 11).

To the best of our knowledge, this represents the best result in the literature in terms of catalyst activity for this kind of reactions, with a turnover number (TON) value of 170, that is at least ten or twenty times higher than that of the analogous reactions.[12,13,19,20] Interestingly, good yields were also achieved with a temperature of 90 °C, that is lower than that commonly adopted (100–120 °C), but with the drawback of requiring too much long times (Table 1, run 12). The ratio between reagents was also surveyed, establishing that twofold quantities of benzoic acid respect to styrene are preferable for carrying a smooth process, while with a 1:1 ratio, the homocoupling of styrene takes place as a side-reaction (Table 1, run 13).

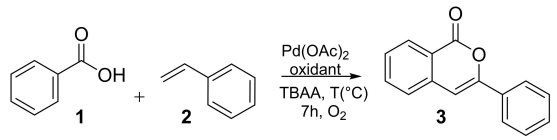
Next, the screening of the reoxidant for palladium catalyst was also conducted. Pd-catalyzed aerobic oxidative reactions using molecular oxygen as the terminal oxidant play a significant role in organic synthesis and many additives have been proposed. Among them, benzoquinone,[21] manganese,[22] iron[23] and copper[18] salts were monitored (Table 2). Accordingly with our previous findings, $Cu(OAc)_2$ showed the best activity in terms of final yields (Table 2 runs 9–12). Additionally, even the presence of molecular oxygen assumed a certain importance since yields were lower when reaction was conducted under air instead of under O_2 atmosphere (Table 2 runs 9–10).

This is in line with results reported in our previous work on the synthesis of cyclopropane,[18] where we suggested that oxygen can act as a terminal oxidant towards palladium while Cu^{+2} operates as an electron-transfer mediator in the reoxidation of Pd^0.

However, as already described by Sthal and Campbell,[24] the use of O_2 as the sole oxidant should be compatible in Pd-catalyzed reactions that proceed via a Pd^{II}/Pd^0 cycle, with a β-hydride elimination in the product-forming step.[24]

Additionally, also the solubility of O_2 in the ionic medium can be an issue to take into account.[25] To this purpose, an attempt was made to couple benzoic acid and styrene under

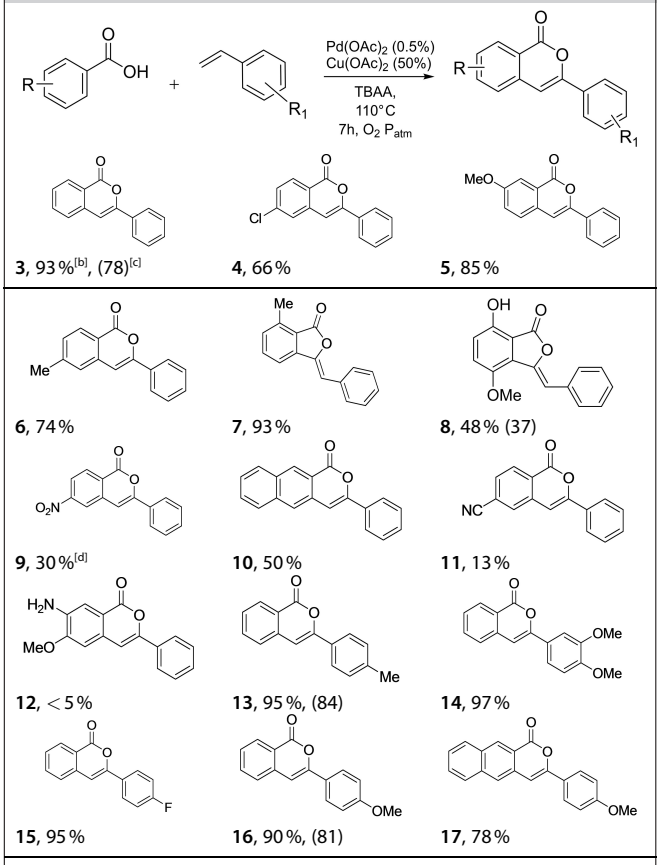
Table 2. Screening of the reoxidant.[a]



Run	Oxidant	Quantity[b] [mol%]	Yield of **3**[c] [%]
1	None[d]	–	8
2	benzoquinone	100	<5
3	$FeSO_4$	100	<5
4	$MnCl_2$	100	<5
5	O_2[e]	1 atm	<5
6	O_2[f]	4 atm	<5 (23)[g]
7	$Cu(SO_4)_2$	100	15
8	$CuCl_2$	100	7
9	$Cu(OAc)_2$[h]	100	68
10	$Cu(OAc)_2$[e]	100	84
11	$Cu(OAc)_2$	50	93
12	$Cu(OAc)_2$	10	37 (50)[g]

[a] Reaction conditions: benzoic acid 5 mmol, styrene 2.5 mmol, IL: 0.5 g, oxidant: 1 equiv., $Pd(OAc)_2$: 0.015 mmol, for 7 h at 110 °C. [b] With respect to styrene. [c] Determined by GC-MS analysis with external standard. [d] Without reoxidant and under nitrogen atmosphere (N_2 balloon reservoir). [e] Under oxygen atmosphere (O_2 balloon reservoir). [f] In autoclave, charged with 4 atm of O_2. [g] Yield at 22 h. [h] Under air.

Table 3. Substrate scope.[a]



[a] Reaction conditions: benzoic acid 5 mmol, styrene 2.5 mmol, TBAA: 0.5 g, $Cu(OAc)_2$: 0.5 equiv., for 7 h. [b] Yield based on GC-MS analysis with external standard. [c] Isolated yield. [d] 1.5% of $Pd(OAc)_2$ was required.

oxygen pressure (Table 2, run 6). Although the direct reoxidation with O_2 could be a feasible route, a modest yield in the isocoumarin highlighted the importance of copper as mediator in the palladium oxidation.

Moreover, since molten TBAA proved to be a good reducing agent for palladium[26] and the formation of Pd(0) aggregates is commonly accepted as an important deactivation pathway,[27] a stoichiometric amount of reoxidant could be necessary.

Remarkably, under our conditions, a sub-stoichiometric amount of $Cu(OAc)_2$ (50 mol%) is required to get acceptable yields in reasonable times (Table 2, run 11). Indeed, reaction can be also accomplished with only 10 mol% of $Cu(OAc)_2$ but longer reaction time is needed and with lower yield (Table 2, run 12).

Even the nature of the anion seems to play a crucial role, since copper salts diverse from acetate furnished disappointing results (Table 2, runs 7–8).

With the optimized conditions in hands, the substrate scope was explored to evaluate both application field and limitations of the method. Data in Table 3 show that catalyst system was active with several substituted benzoic acids and styrenes leading to 3-arylisocoumarins **3**–**17** in good yields. A close inspection on the effect of the substituents, reveals a mechanism compatible with an electrophilic aromatic substitution (S_EAr).[13] Indeed, better results were generally obtained with benzoic acids bearing electron donating groups (e.g. isocoumarins **3**,**5**,**6**,**7**,**15**,**16**,**17**), a moderate yield was achieved with *p*-chlorobenzoic acid (**4**, 66%), while relatively inert proved to be benzoic acids possessing electron withdrawing substituents (e.g. isocoumarins **9**,**11**).

Inhibiting effects were somehow exerted by hydroxyl and amino groups on the aromatic ring, as revealed by the moderate to very low yields obtained for isocoumarins **8** and **12**, most probably due to the susceptibility of substituents to oxidation.

A special behavior was observed in the case of *ortho*-toluic acid, that afforded high yields of (*Z*)-3-benzylidene-7-methylisobenzofuran-1(3H)-one **7** instead of isocoumarin, but the rationale for this different regiochemistry, as already reported, is still under investigation.[12,13]

Concerning the selectivity of the reaction, this is generally very high, providing only the desired product. However, when deactivated vinyl arenes were used, or for prolonged reaction times, the presence of small amounts (usually less than 5%) of the saturated product can be detected by GC-MS analyses. This is probably due to the re-addition of H–Pd-H to the double bond of the isocoumarine, after its formation. Furthermore, for longer reaction times and higher temperatures, tributylamine can also be found, due to the retro-quaternization of the ammonium salt (Hofmann's elimination), as reported in our previous works dealing with tetraalkylammonium ionic liquids.[14,16]

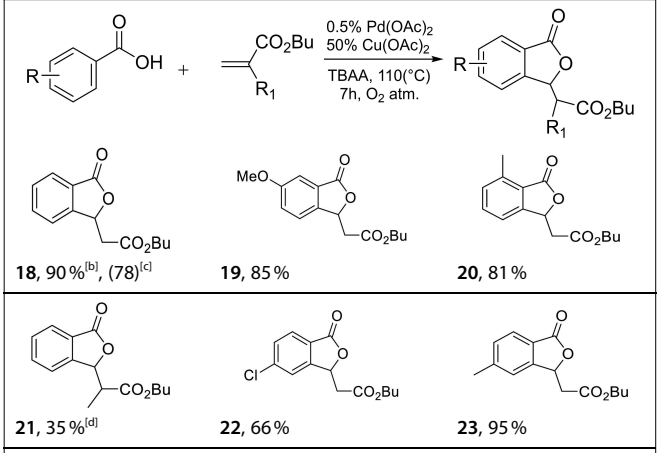
To widen the scope of the method, other vinyl compounds were tested as an alternative to styrenes. Unfortunately, alkyl olefines as well as alkyl and phenyl vinyl ethers proved to be unreactive (data not shown). On the contrary, when styrene was replaced with acrylates, under our conditions, phthalides were

achieved in good yields. Representative results are summarized in Table 4.

The phthalide skeleton is present in a large number of natural products with important biological properties, such as anti-thrombosis, anti-platelet accumulation, activity on the central nervous system, modulation of myocardial contraction, protection against cerebral ischemia, and anti-angina.[28,29]

A plethora of synthetic protocols based on Ru and Rh-catalyzed C–H olefination of benzoic acids is available in the literature,[30,31] and, in the last years, thanks to works by Ackermann's group, the preparation of isobenzofuranone derivatives has received great attention.[19,32–34]

Table 4. Synthesis of phthalides.[a]



[a] Reaction conditions: benzoic acid 5 mmol, acrylate 2.5 mmol, TBAA: 0.5 g, $Cu(OAc)_2$: 0.5 equiv., for 7 h. [b] Yield based on GC-MS analysis with external standard. [c] Isolated yield. [d] Mixture of diastereoisomers.

Under our conditions, also ligand-free palladium acetate proved to be an effective catalyst and various phthalides can be achieved in good yields. Even a hindered olefin such as butyl methacrylate can be reacted even with more modest yields (Table 4, **21**). Concerning the catalytic cycle, in 1998, Miura and co-workers proposed a mechanism based on Pd(II)/Pd(0) species. The formation of isocoumarins and benzylidenephthalides is explained by assuming the initial *ortho* C–H activation onto benzoic acid that leads to a cyclopalladate intermediate **A** (Figure 1).[12] A five- or a six-membered ring can be formed after the migratory insertion onto the olefin, depending on the presence of a substituent on the *ortho* position of the benzoic acid.

The formation of the five membered palladacycle was also postulated by Lee et al. in 2013, then followed by a β-migratory insertion of the vinylarene. Next, an intramolecular attack of the carboxylate on C_1 or C_2 of the vinyl group can afford, under steric control, isocoumarins or phthalides.[13]

The same authors also performed kinetic isotopic experiments, and a k_H/k_D value of 2.8 pointed out a plausible rate determining step involving the *ortho* aryl C–H activation.[13]

In order to gain insights regarding the catalytic cycle, we focused our attention on the palladacycle (**A**) derived from the *ortho* C–H activation. Firstly, we tried the synthesis, under our conditions, of a styrylbenzoate (*ortho* or *para*) as depicted in Scheme 2.

Detection of small percentages of **3** (5%) together with trace amounts of benzoic acid in the reaction mixture, associated with the total absence of the desired product, confirmed the importance of the presence of the carboxylic group[35] and the plausible formation of cyclopalladate intermediate **A** in the first step of the catalytic cycle. Consequently, palladium can activate selectively the C–H *ortho* position due to the spatial proximity of the metal center to the C_2 of the benzoic acid. Unfortunately, all the attempts made to gain direct evidence of the formation of **A** by monitoring the reaction mixture by ESI-HRMS were disappointed.

Regarding the role of the ionic liquid, and in particular of TBAA, as already mentioned, better results can be obtained with tetraalkylammonium salts instead of classical RTILs. Yu et al. in 2008 showed that the presence of tetrabutylammonium salt can accelerate the C–H bond cleavage through the formation of a tetrabutylammonium benzoate ion pair in the *ortho* halogenation of benzoic acids catalyzed by palladium acetate.[36] Indeed, the presence of NR_4^+ cations can also favor the K^I-coordination of Pd to benzoic acid, assisting the *ortho* C–H activation.[37] Moreover, due to the need for a base in the

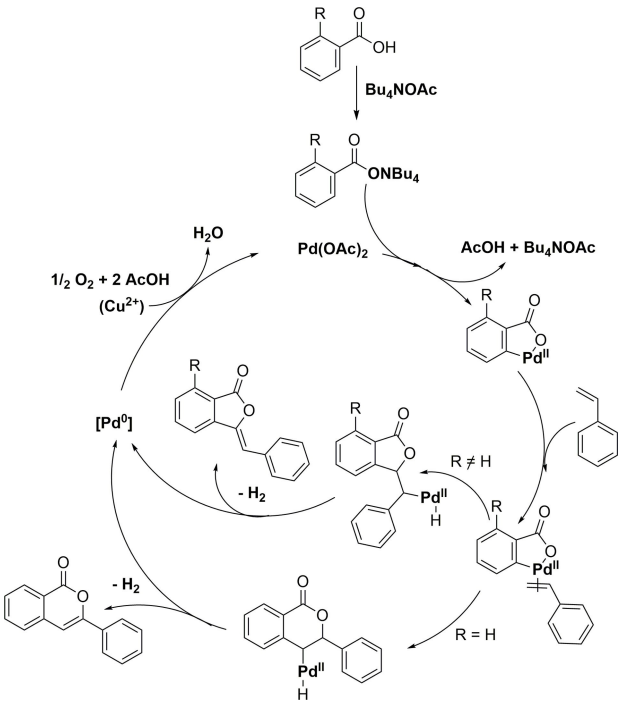
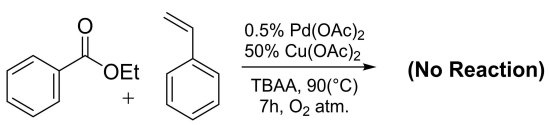


Figure 1. Generally proposed mechanism.



Scheme 2. Palladium catalyzed synthesis of ethyl-2-styrylbenzoate.

reaction mechanism, the nature of the anion seems to play a crucial role since counterion different from acetate, gave lower or no results.

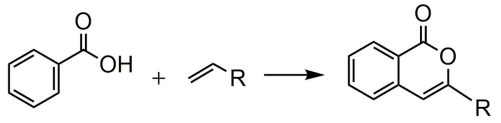
Same conclusions can be invoked for the role of copper acetate that can act as a mediator for the reoxidation of Pd, as a base and can also probably promote the styrene insertion by coordination of this latter. Based on these outcomes, we proposed the reaction mechanism presented in Figure 1.

Even if a Pd(II)/Pd(IV) mechanism cannot be completely ruled out,[36,38] a catalytic cycle oscillating between Pd(0)/Pd(II) is generally accepted in this kind of reaction.[12,13,35,39]

Conclusion

In conclusion, a straightforward protocol for Pd-catalysed oxidative coupling of benzoic acids with vinyl arenes and acrylates, leading to isocoumarins and phthalides, was proposed for the first time in ionic liquid as the reaction medium (TBAA). This latter exerts a strong beneficial effect allowing to drop palladium loading until to 0.5 mol%, which is ten to twenty times lower than that of similar protocols in molecular solvents (Scheme 3).

Besides the twentyfold turnover number compared to literature, other advantages of this method stem from avoiding the use of stoichiometric amounts of expensive silver-based reoxidants and toxic solvents like DMF and MeCN. In addition, a simple ligandless Pd acetate salt is used in place of more expensive Rh or Ru complexes bearing special ligands.



Previous works	Lit.
a $Pd(OAc)_2$ 10%/$Cu(OAc)_2$ 10%, 100 °C, 10 h, N_2-air, DMF, MS 4A	Miura et al. 1998 [12]
b $Pd(OAc)_2$ 10% Ag_2CO_3 (2 equiv) MeCN	Huang, Zhao et al. 2013 [20]
c $Pd(OAc)_2$ 5% Ag_2O (1 equiv), 110 °C, 20 h, air, DMF, MS 4A	Lee et al. 2013 [13]
This work	
d $Pd(OAc)_2$ 0.5% / $Cu(OAc)_2$ 50% 110 °C, 7 h, TBAA, O_2 P_{atm}	

Scheme 3. Comparison with Pd-catalysed methods in the literature.

Twenty examples of 3-aryl substituted isocoumarins and phthalides are reported, with high yields in most cases. Studies are still in progress to further lower copper acetate to minimal amounts using oxygen as the only true oxidant.

Experimental Section

General procedure for synthesis of isocoumarins and phthalides: In a 5 mL vial having a side-arm connected to an oxygen balloon reservoir and equipped with a screw cap and a magnetic bar, 0.5 g of TBAA, 5 mmol of benzoic acids, 2.5 mmol of styrene, $Pd(OAc)_2$ (0.5 mol%), $Cu(OAc)_2$ (2.5 mmol) were added. The mixture was heated under stirring at 110 °C for the proper reaction times depending on the substrate (generally 7 h). For the products identification preliminary GC-MS analyses were performed by treating weighed aliquots of reaction mixture with aqueous HCl, then extracted with ethyl acetate. To evaluate yields of isocoumarins (table 3) and phthalides (table 4) and to assure the identification of the main reaction products, the whole reaction mixture was washed with aqueous HCl and extracted with ethyl acetate. Then, the combined organic layers were dried over anhydrous MgSO4, the solvent removed in vacuo and the crude mixture was chromatographed on silica gel (eluent hexane/ethyl acetate). The isolated products were identified by NMR, GC-MS and ESI-HRMS analyses.

The procedures and the data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

We gratefully acknowledge the PON project Research and Innovation (2014–2020) ECOTEC_ARS 01_00951 for financial support. Open Access funding provided by Università degli Studi di Bari Aldo Moro within the CRUI-CARE Agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: benzylidenephthalide · C–H activation · isocoumarin · ionic liquid · palladium catalysis

[1] Z. Xu, Q. Chen, Y. Zhang, C. Liang, *Fitoterapia* **2021**, *150*, 104863.
[2] A. Saeed, *Eur. J. Med. Chem.* **2016**, *116*, 290–317.
[3] R. M. Iacobazzi, C. Annese, A. Azzariti, L. D'Accolti, M. Franco, C. Fusco, G. La Piana, V. Laquintana, N. Denora, *ACS Med. Chem. Lett.* **2013**, *4*, 1189–1192.
[4] A. Saeed, *J. Chin. Chem. Soc.* **2003**, *50*, 313–317.
[5] S. Pal, M. Pal, *Synthesis of Isocoumarins* **2019**.
[6] L. Dai, S. Yu, W. Xiong, Z. Chen, T. Xu, Y. Shao, J. Chen, *Adv. Synth. Catal.* **2020**, 1893–1898.
[7] S. Pal, V. Chatare, M. Pal, *Curr. Org. Chem.* **2011**, *15*, 782–800.

[8] Y. H. Wang, G. Qiu, H. Zhou, W. Xie, J. B. Liu, *Tetrahedron* **2019**, *75*, 3850–3855.
[9] J. Son, C. Maeng, P. H. Lee, *Bull. Korean Chem. Soc.* **2020**, *41*, 388–399.
[10] P. Saikia, S. Gogoi, *Adv. Synth. Catal.* **2018**, *360*, 2063–2075.
[11] R. C. Larock, S. Varaprath, H. H. Lau, C. A. Fellows, *J. Am. Chem. Soc.* **1984**, *106*, 5274–5284.
[12] M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem.* **1998**, *63*, 5211–5215.
[13] D. Nandi, D. Ghosh, S.-J. Chen, B.-C. Kuo, N. M. Wang, H. M. Lee, *J. Org. Chem.* **2013**, *78*, 3445–3451.
[14] V. Calò, A. Nacci, A. Monopoli, A. Damascelli, E. Ieva, N. Cioffi, *J. Organomet. Chem.* **2007**, *692*, 4397–4401.
[15] A. Monopoli, M. Casiello, C. Fusco, L. D'Accolti, F. Iannone, A. Nacci, *J. Organomet. Chem.* **2022**, *958*, 122193.
[16] V. Calò, A. Nacci, A. Monopoli, *Eur. J. Org. Chem.* **2006**, 3791–3802.
[17] P. Mastrorilli, A. Monopoli, M. M. Dell'Anna, M. Latronico, P. Cotugno, A. Nacci, in *Top. Organomet. Chem.* **2015**, pp. 237–286.
[18] P. Cotugno, A. Monopoli, F. Ciminale, A. Milella, A. Nacci, *Angew. Chem. Int. Ed.* **2014**, *53*, 13563–13567; *Angew. Chem.* **2014**, *126*, 13781–13785.
[19] Y. Qiu, M. Stangier, T. H. Meyer, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14179–14183; *Angew. Chem.* **2018**, *130*, 14375–14379.
[20] D. Yang, S. Ding, J. Huang, K. Zhao, *Chem. Commun.* **2013**, *49*, 1211–1213.
[21] W. J. Kong, M. Reil, L. Feng, M. B. Li, J. E. Bäckvall, *CCS Chem.* **2021**, *3*, 1127–1137.
[22] W. Zhang, N.-X. Wang, C.-B. Bai, Y.-J. Wang, X.-W. Lan, Y. Xing, Y.-H. Li, J.-L. Wen, *Sci. Rep.* **2015**, *5*, 15250.
[23] R. A. Fernandes, D. A. Chaudhari, *J. Org. Chem.* **2014**, *79*, 5787–5793.
[24] A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851–863.
[25] B. A. Steinhoff, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355.
[26] V. Caló, A. Nacci, A. Monopoli, S. Laera, N. Cioffi, *J. Org. Chem.* **2003**, *68*, 2929–2933.
[27] N. Van Velthoven, S. Waitschat, S. M. Chavan, P. Liu, S. Smolders, J. Vercammen, B. Bueken, S. Bals, K. P. Lillerud, D. E. De Vos, *Chem. Sci.* **2020**, 3616–3622.
[28] T. Saito, T. Itabashi, D. Wakana, H. Takeda, T. Yaguchi, K. Kawai, T. Hosoe, *J. Antibiot.* **2016**, *69*, 89–96.
[29] R. A. Limaye, V. B. Kumbhar, A. D. Natu, M. V. Paradkar, V. S. Honmore, R. R. Chauhan, S. P. Gample, D. Sarkar, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 711–714.
[30] A. Awasthi, M. Singh, G. Rathee, R. Chandra, *RSC Adv.* **2020**, *10*, 12626–12652.
[31] H. Zhao, T. Zhang, T. Yan, M. Cai, *J. Org. Chem.* **2015**, *80*, 8849–8855.
[32] I. Choi, A. M. Messinis, X. Hou, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 27005–27012.
[33] Y. Qiu, W.-J. Kong, J. Struwe, N. Sauermann, T. Rogge, A. Scheremetjew, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5828–5832; *Angew. Chem.* **2018**, *130*, 5930–5934.
[34] A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264–267; *Angew. Chem.* **2016**, *128*, 272–275.
[35] J. Das, D. K. Mal, S. Maji, D. Maiti, *ACS Catal.* **2021**, *11*, 4205–4229.
[36] T. Mei, R. Giri, N. Maugel, J. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215–5219; *Angew. Chem.* **2008**, *120*, 5293–5297.
[37] S. Li, H. Wang, Y. Weng, G. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 18502–18507; *Angew. Chem.* **2019**, *131*, 18673–18678.
[38] K. Muñiz, *Angew. Chem. Int. Ed.* **2009**, *48*, 9412–9423; *Angew. Chem.* **2009**, *121*, 9576–9588.
[39] A. Saeed, M. Haroon, F. Muhammad, F. A. Larik, E. S. Hesham, P. A. Channar, *J. Organomet. Chem.* **2017**, *834*, 88–103.

Manuscript received: July 28, 2022
Accepted manuscript online: August 23, 2022
Version of record online: September 19, 2022