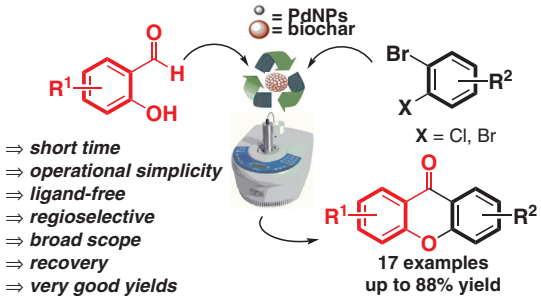
Synthesis H. S. Steingruber et al. Paper

A Green Nanopalladium-Supported Catalyst for the Microwave-Assisted Direct Synthesis of Xanthones

H. Sebastián Steingruber
Pamela Mendioroz
Alejandra S. Diez
Darío C. Gerbino*

Instituto de Química del Sur, INQUISUR (CONICET-UNS), Departamento de Química, Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina
dgerbino@uns.edu.ar



Received: 03.09.2019
Accepted after revision: 10.10.2019
Published online: 30.10.2019
DOI: 10.1055/s-0039-1691069; Art ID: ss-2019-m0507-op

Abstract We report an efficient, selective, rapid and eco-friendly protocol for the one-step synthesis of a small xanthone library via an intermolecular catalytic coupling from readily available salicylaldehydes and 1,2-dihaloarenes under ligand-free conditions. To achieve this advantageous direct annulation, we used a novel recoverable palladium nanocatalyst supported on a green biochar under microwave irradiation. Unlike other existing palladium-based approaches, our synthetic strategy showed a greater operational simplicity, drastic reduction in reaction times, and an excellent tolerance to diverse functional groups. The reaction proceeds in very good yields and with high regioselectivity. The novel heterogeneous catalyst can be recycled and reused up to four times without significant loss of activity.

Key words xanthones, coupling, microwave-assisted synthesis, palladium nanoparticles, green biochar

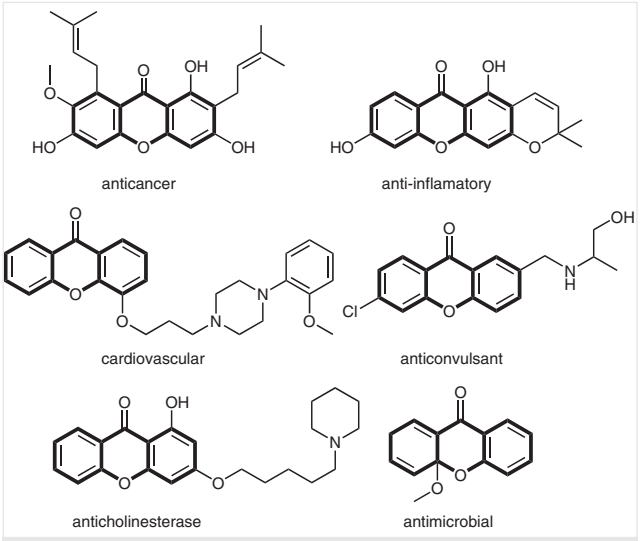


Figure 1 Biological action of a selection of xanthones

Xanthones or 9*H*-xanthen-9-ones constitute a recognized pharmacological unit formed by a dibenzo-γ-pyrone scaffold.[1] Their structure is widely distributed in natural bioactive products.[2] The planar architecture gives this class of oxygenated heterocycles a wide variety of biological activities; among them, the modulatory action of PKC (Protein Kinase C), and other interesting pharmacological properties such as anti-inflammatory, antibacterial, antifungal and antitumor action.[3] The biological role of this class of oxygenated heterocycles can be modulated by the introduction of specific substituents in their skeleton (Figure 1).[4]

Due to its versatile biocompatibility with multiple biological targets, the xanthone skeleton emerges as an interesting synthetic objective in the field of medicinal chemistry. Standard syntheses of this 'privileged' scaffold usually demand multistep procedures, which generally involve the intermediacy of a benzophenone or a diaryl ether, and often suffer from harsh reaction conditions, poor functional-group tolerance, and/or strong acids or toxic metals are often employed.[5]

In the last decade, a diversification of methods for the direct synthesis of xanthones has been reported, but most protocols require complex precursors, drastic reaction conditions, expensive non-recoverable catalysts, and the presence of phosphine ligands and/or additives.[6] Therefore, the development of a new and more efficient synthetic route that results in reduced waste and that requires fewer steps is highly desirable.

In recent years, there has been growing interest in the development of highly efficient and selective catalysts based on transition metals, mainly due to atom economy, low toxicity, atom efficiency and eco-friendliness, which are essential from the perspective of green chemistry. In

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

this sense, the use of new nanocatalysts that have high activity, low cost and that are easily recoverable, constitutes an attractive green strategy for the construction of compound libraries of medicinal scaffolds in the pharmaceutical industry.[7]

Microwave-assisted organic synthesis (MAOS) is a powerful and versatile tool that can be applied to a wide range of chemical reactions, enabling advantages such as shorter reaction times, higher yields, limited generation of byproducts and the relatively easy scale-up without detrimental effects.[8]

The use of microwaves in conjunction with metal catalysts offers significant advantages over traditional methods, since the temperature gradient reversal under microwave conditions leads to increased catalyst life through the elimination of the effect of wall.[9]

For several years, we have been focused on the search for new and more efficient eco-friendly protocols aimed at the one-step synthesis of xanthones and structurally related analogues.[4a,10]

In 2014, our research group developed an efficient and versatile strategy for the construction of the xanthonic skeleton through a ligand-free intermolecular catalytic coupling from *ortho*-substituted benzaldehydes and a wide range of phenols. For this purpose, we use a novel heterogeneous copper nanocatalyst supported on a magnetic inorganic material (Magsilica).[10c]

In recent years, palladium-catalyzed acylation of aryl halides with 2-substituted benzaldehydes has emerged as an alternative method for the generation of xanthones and their congeners.[11]

To our knowledge, only two direct syntheses of xanthones via Pd-catalyzed annulation of 1,2-dihaloarenes and salicylaldehydes as starting materials have been reported.[6d,e] The main difficulties encountered in the two synthetic routes catalyzed by palladium involve the need to use activated salicylaldehydes (presence of electron-donor groups), high reaction times (12 h), the presence of phosphine ligands, and the impractical recovery and reuse of the catalyst.

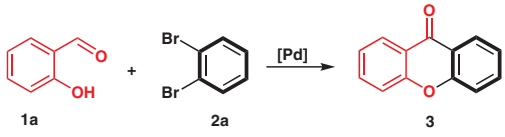
Inspired by these results, herein we disclose an alternative, rapid and convenient coupling reaction of aryl dihalides with functionalized salicylaldehydes that is catalyzed by heterogeneous palladium, which provides one-step access to a small library of xanthones under microwave irradiation. To achieve this goal, we present a novel heterogeneous catalyst that is constituted of palladium nanoparticles supported on biochar (henceforth referred to as PdNPs/BC), which was obtained as a byproduct from the pyrolysis of the sunflower seed hull.[12]

In 2009, Peng and co-workers reported a one-step synthesis of xanthones through intermolecular coupling of 1,2-dibromoarenes with diverse salicylaldehydes in DMF at 130 °C in the presence of a homogeneous $PdCl_2(PPh_3)_2$ catalyst using K_2CO_3 as base.[6e] More recently, Shen and Wu developed a selective protocol for the direct generation of xanthones from commercially available 2-bromofluorobenzenes and salicylaldehydes by utilizing $Pd(OAc)_2$ as the catalyst in the presence of phosphine ligands.[6d]

Based on this knowledge, and as part of our interest in the area of palladium-catalyzed coupling reactions, we examined a new methodology with the purpose of developing a reliable, eco-friendly and operationally more effective protocol for the direct construction of the xanthone scaffold through the use of a novel heterogeneous palladium nanocatalyst, from readily available starting materials under microwave and thermal conditions.

The reaction conditions for the palladium-catalyzed intermolecular annulation reaction were optimized by using salicylaldehyde (**1a**) and 1,2-dibromobenzene (**2a**) as model substrates (Table 1). In a first set of control experiments, we evaluated the catalytic activity of six heterogeneous and homogeneous palladium-based catalysts under the reaction conditions proposed by Peng {[Pd] (5 mol%), DMF, K_2CO_3, 130 °C, 12 h).[6e] Taking into account the extended reaction times, we investigated the use of microwave irradiation to reduce reaction times and improve the efficiency of the process.

Table 1 Preliminary Screening of Pd Catalysts[a]



1a 2a 3

Entry	[Pd]	*T* (°C)	Yield (%)[c]	
			Thermal[a]	Microwave[b]
1	–	130	–	–
2	PdNPs/BC	130	15	44
3	PdNPs/BC	150	46	89
4	PdNPs/BC	150	44	88[d]
5	PdNPs	130	–	12
6	PdNPs	150	trace	25
7	$PdNPs/Al_2O_3$	130	trace	18
8	$PdNPs/Al_2O_3$	150	trace	25
9	PdNPs/PbO	130	trace	10
10	$PdCl_2(PPh_3)_2$	130	61	48
11	$PdCl_2(PPh_3)_2$	150	trace[e]	–
12	$Pd(OAc)_2$	130	–	–
13	$PdCl_2(MeCN)_2$	130	–	–

[a] Reaction conditions: Salicylaldehyde **1a** (1 mmol), 1,2-dibromobenzene **2a** (2 mmol), [Pd] catalyst (5 mol%), K_2CO_3 (2 mmol) in DMF (5 mL), 12 h.
[b] Reaction was conducted at 250 W, 30 min. Time reaction monitored by TLC and GC-MS.
[c] Isolated yield.
[d] Reaction performed using 3 mol% of PdNPs/BC catalyst.
[e] Deposition of black palladium was observed.

Reaction progress was not detected in the absence of catalyst (Table 1, entry 1). To our satisfaction, when our novel PdNPs/BC was used under microwave irradiation (250 W, 130 °C), the progress of reaction was evident even at very short reaction times of 30 minutes (entry 2). In contrast, when the reaction was performed under thermal conditions, a low yield of **3** (15%) was detected after 12 hours. Surprisingly, a significant increase in the formation of the xanthone scaffold was observed when the reaction was subjected to microwave irradiation at 150 °C (entry 3). On the other hand, the catalytic activity mediated by unsupported palladium nanoparticles under thermal conditions (entries 5 and 6) did not lead to the formation of the expected product. Reaction progress (25%) was observed in the same catalytic system under microwave irradiation at 150 °C (entry 6).

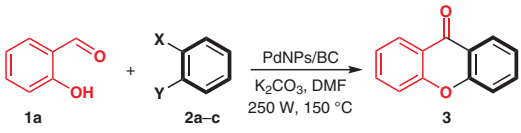
Other palladium nanocatalysts supported on inorganic materials such as Al_2O_3 (Table 1, entry 8) and PbO (entry 9) enabled access to **3** with poor yields under microwave irradiation. In this case, the increase in temperature did not lead to an improvement in terms of conversion into the base skeleton of xanthone. It was observed that PdNPs/BC exhibited the best results as catalyst in the desired transformation (entry 4), whereas $PdCl_2(PPh_3)_2$ showed less catalytic yield. The use of some commercial palladium catalysts (entries 9–11) did not lead to an improvement in the generation of **3** under the reaction conditions studied. No product formation was observed by use of other commercial homogeneous palladium catalysts such as $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ (entries 12 and 13).

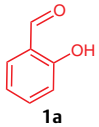
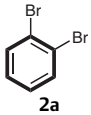
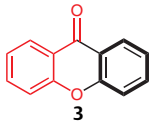
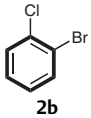
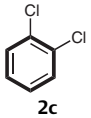
We then optimized the biochar supported nanocatalyst loading under microwave irradiation at 250 watts of power and 150 °C. As shown in Table 1, we started our study by using 5 mol% of PdNPs/BC, thus obtaining the desired product **3** in 89% yield. We were delighted to find that the reaction proceeded with the same efficiency and selectivity by using a catalyst loading as low as 3 mol% of PdNPs/BC. Loading of the catalyst to less than 3 mol% proved to be unsatisfactory in terms of yields, and loading more than 5 mol% did not improve reaction times or yield significantly. Having defined the nature and charge of the palladium catalyst, we then proceeded to explore the incidence of microwave irradiation on the reaction at power values of 100, 200, 250 and 300 W. For this purpose, we used a focused CEM-Discover reactor at 150 °C. Reactions were monitored by TLC and GC-MS at different times. The complete conversion of the starting salicylaldehyde was observed after 30 min at 250 W and 150 °C. It should be noted that a shorter reaction time (for example, 20 minutes) led to incomplete transformation of the starting materials, while an increase in time of up to 40 min or more did not result in an improvement in terms of performance. Microwave irradiation at 100, 200 and 300 W power led to lower conversions of the starting materials and reaction times of more than 30 minutes. In this way, we were able to conclude that the best power of MW in terms of yields and speed of product formation was 250 W at 150 °C.

The use of other solvents such as *N*,*N*-dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP) and DMSO did not improve the reaction. On the other hand, the use of less polar solvents such as toluene or dioxane led to minimum conversion.

Additionally, a screening of different bases such as K_2CO_3, K_3PO_4, Na_2CO_3 and Cs_2CO_3 was examined (see Supporting Information for experimental details). A control reaction carried out without base led to trace amounts of the desired product. Of all the bases tested, it was found that K_2CO_3 was the most effective. From these studies, it was found that the optimal reaction conditions for the direct synthesis of xanthone **3** requires the use of salicylaldehyde (1 mmol), 1,2-dibromobenzene (2 mmol), PdNPs/BC (3 mol%, 4 mg of Pd) as a catalyst, K_2CO_3 (2 mmol, with respect to the starting salicylaldehyde) and DMF (5 mL) at 150 °C under microwave irradiation (250 W) for 30 minutes. Remarkably, under the optimized reaction conditions, the presence of phosphine ligands and/or additives was not necessary for the successful progress of the reaction. It is also important to note that the formation of the biaryl byproduct was not detected by palladium-catalyzed homocoupling of **2a**, which denotes the selectivity of the present methodology towards the direct annulation of **1a** with **2a**.

Table 2 Substrate Scope for the Synthesis of 9*H*-Xanthen-9-one **3**[a]



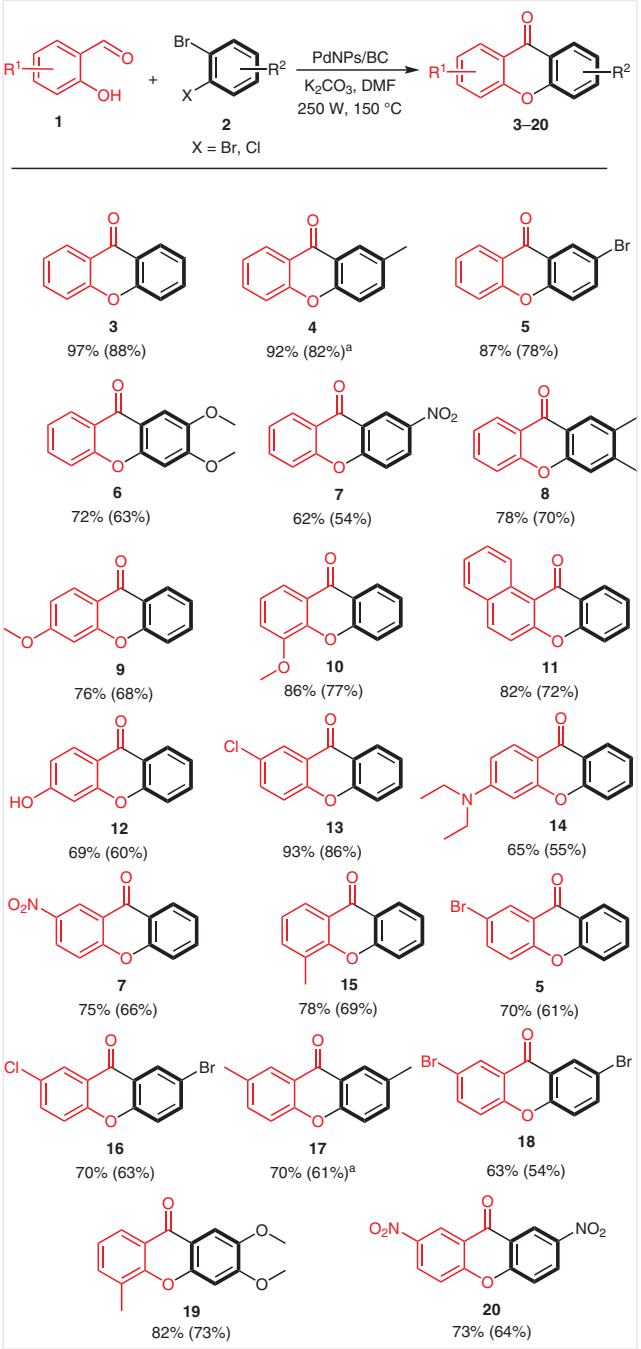
Entry	Salicylaldehyde	1,2-Dihalobenzene	Xanthone	Yield (%)[b]
1	 **1a**	 **2a**	 **3**	88
2	**1a**	 **2b**	**3**	82
3	**1a**	 **2c**	**3**	67

[a] Reaction conditions: salicylaldehyde (1 mmol), *ortho*-dihalobenzene (2 mmol), PdNPs/BC (3 mol%), K_2CO_3 (2 mmol) in DMF (5 mL) at 150 °C under MW (250 W) for 30 min.
[b] Isolated yield.

To evaluate the scope of substrate, different 1,2-dihalobenzenes were evaluated by reaction with 2-hydroxybenzaldehyde (**1a**) under the optimized conditions. As illustrated in Table 2, the respective 1,2-dihalobenzenes **2a–c** led to the xanthone scaffold **3** with good to very good yields (67–88%). Notably, this catalytic system was not limited to the use of bromides as leaving groups (entry 1), but also allowed the use of less reactive chlorinated benzenes (entries 2 and 3). Of the different halogens tested as leaving groups, bromo group gave the highest yields.

With the optimized conditions in hand, we then explored the scope, limitations and the general efficiency of the one-step annulation protocol by reaction of 1,2-dihaloarenes with different salicylaldehydes; the results are summarized in Scheme 1. The results clearly demonstrate that the new synthetic methodology is compatible with the presence of a variety of functional groups in the starting salicylaldehydes, including nitro, bromo, chloro, methoxy, alkyl, alkyl amino and a free phenolic hydroxyl group, affording the desired xanthones in good to excellent conversions (**5**, **7** and **9–15**). However, when a strong electron-donating group such as diethylamino and hydroxyl were introduced, the yields of isolated products decreased to 55% (**14**) and 60% (**12**), respectively. The reaction conditions showed a good tolerance to the presence of electron-rich or electron-deficient groups in the starting symmetrically substituted 1,2-dihaloarenes, leading to the formation of the expected xanthones with good to very good yields (**4–8** and **19**). Additionally, we evaluated the chemo- and regioselectivity of our synthetic methodology by using unsymmetrically substituted 1,2-dihaloarenes (Scheme 1).[13] Thus, the intermolecular annulation of 2-bromo-1-chloro-4-methylbenzene bearing both a bromo and a chloro substituent occurred chemo- and regioselectively, leading to xanthone **4** in very good yield. To our satisfaction, high regioselectivities were also observed when using unsymmetrically substituted 1,2-dibromobenzenes as substrates. It was found that the intramolecular O-arylation of 4-NO_2 and 4-Br substituted 1,2-dibromobenzenes occurred selectively at the *para*-position (**5**, **7**, **16**, **18** and **20**). On the other hand, when 1,2-dibromo-4-methylbenzene was reacted with functionalized salicylaldehydes, an isomeric ratio of about 1:1 was identified by ^{1}H NMR spectroscopic analysis of the crude product, which indicates in this case in particular the low control of regioselectivity.

It should be noted that the use of our new heterogeneous palladium nanocatalyst based on a novel green biochar support, allowed the direct synthesis of xanthones from salicylaldehydes and 1,2-dihaloarenes with strong electron-withdrawing groups (**7** and **20**), thus overcoming one of the limitations reported by the Peng and Wu groups. Under these reaction conditions, byproducts from the coupling of the 1,2-dihaloarenes were not observed. The work-up and isolation of crude product consisted of adding ethyl acetate to the reaction mixture. The catalyst was recovered



Scheme 1 Scope for the direct synthesis of functionalized xanthones. *Reagents and conditions*: salicylaldehyde (1 mmol), 1,2-dibromobenzene (2 mmol), K_2CO_3 (2 mmol), PdNPs/BC (3 mol%) in DMF at 150 °C under microwave irradiation (250 W) for 30 min. Quantified by GC analysis using internal standard method. Isolated yield after purification (in parentheses). [a] The reaction was conducted in the presence of 2-bromo-1-chloro-4-methylbenzene. When 1,2-dibromo-4-methylbenzene was reacted, an isomeric ratio of about 1:1 was detected by ^{1}H NMR analysis of the crude product.

by filtration and washed several times with the same solvent. The filtrate was washed twice with a saturated solution of NaCl and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the desired product was purified by column chromatography using silica gel 60 as adsorbent. The structures of all synthesized xanthones **3–20** were confirmed based on their spectroscopic data, as provided in the Supporting Information.

To check the recyclability of the PdNPs/BC catalyst, we selected the one-step synthesis of xanthone **3** as model reaction under the optimized reaction conditions. The results are reported in Figure 2. After completion of the reaction (monitoring by TLC), the nanocatalyst was easily separated from the reaction mixture by filtration and washed several times with EtOAc and then dried under vacuum to be used directly for further catalytic reactions. No significant loss of catalytic efficiency was observed up to four cycles.

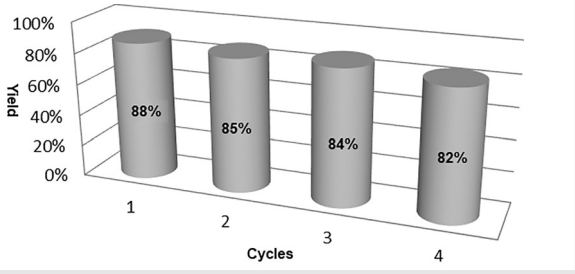


Figure 2 Recyclability of the PdNPs/BC catalyst in the one-step synthesis of xanthone **3**

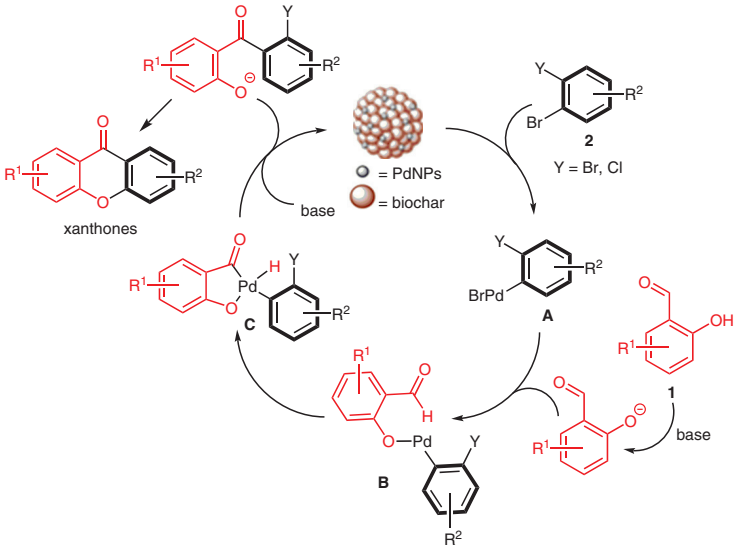
The low diminution in the activity from the first to the fourth cycle is consistent with the small losses of catalyst mass during the washing procedure.

The recycled catalyst was checked by X-ray diffraction (XRD) analysis, and it was found that there was no change in the catalyst pattern before and after the reaction, showing that the nature of the PdNPs/BC was not modified under the reaction conditions. For both fresh and spent catalyst, the XRD pattern was consistent with standard values of PdNPs/BC, which confirmed that the PdNPs did not change before and after the reaction.

Next, the leaching of metal from the PdNPs/BC was studied. After the separation, the filtrate was analyzed by atomic absorption spectroscopy (AAS); it was found that 0.001% of the metal leached into the solution after the second cycle. This study clearly demonstrated that there was no significant amount of leaching. It is also observed from spectral studies that there was no change in the nature of the catalyst even after four cycles.

On the basis of the results obtained, a plausible mechanism is proposed in Scheme 2.[6d,e,14] 1,2-Dihaloarene **2** first undergoes oxidative addition of palladium(0) catalyst. Then, the aryl–palladium(II) intermediate **A** reacts with salicylate **1** generated under basic conditions by displacing the halide and leading to the formation of aryl(aryloxy) palladium(II) intermediate **B**. Subsequently, **B** would undergo a C–H activation through the C–H bond of the aldehyde to give the intermediate cyclic palladium **C**.[15] Finally, β-elimination of **C** followed by an intramolecular nucleophilic substitution would lead to the desired xanthone.

In summary, we have developed a new eco-friendly methodology for the direct, selective and rapid construction of functionalized xanthones from readily available starting materials by using a novel catalytic system based on PdNPs supported on a green biochar. MAOS allowed to significantly reduce the reaction time to minutes as compared to previously reported conventional heating for



Scheme 2 Proposed catalytic cycle for the PdNPs-catalyzed direct synthesis of xanthones

longer times to synthesize xanthones and closely related analogues. Additionally, our proposed protocol showed excellent tolerance to diverse functional groups and did not require the presence of ligands or additives, unlike other palladium-based approaches. Moreover, a small library of xanthones could be generated with very good average yields and with excellent control of regioselectivity.

The novel heterogeneous catalyst could be reused four times with minimal loss in activity. The easy recovery of the catalyst, together with the negligible leaching of metallic species (0.001% of palladium was detected by AAS) in the studied transformation, makes this methodology especially attractive from a green chemistry perspective. The scalable potential of the process, together with the simple reaction conditions, wide functional diversity and low cost of the starting materials mean that the present protocol could be transferred to the pharmaceutical industry.

Efforts to expand the utility of this reaction and detailed mechanistic works based on DFT calculations are ongoing in our research group.

Unless otherwise noted, reagents were obtained commercially and used without further purification. Solvents were dried and distilled in accordance with standard procedure.[16] Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. All ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 with a Bruker Avance ARX-300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: δ = 7.26 ppm for ^{1}H NMR, δ = 77.16 ppm for ^{13}C NMR). Multiplicities are abbreviated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal. IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer in the ATR mode at room temperature. Melting points were determined with a Büchi 510 apparatus and are not corrected. Mass spectra (EI) were obtained at 70 eV with a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a GC Shimadzu (GC-14B) with a flame-ionization detector equipped with a HP-5MS column (30 m × 0.25 mm × 0.25 µm) using nitrogen as carrier gas. High-resolution mass spectra were recorded with a Thermo Fisher LTQ Orbitrap XL (for EI) and a Finnigen MAT 95 (for ESI). Flash column chromatography was performed with Macherey Nagel MN silica gel 60M (0.040–0.063 mm / 230–240 mesh ASTM). Microwave reactions were performed with a microwave oven CEM Discover in sealed reaction vessels. The palladium loading of the catalyst was determined by atomic absorption spectrometry (AAS) in a Perkin Elmer AAnalyst 700 instrument. Powder X-ray diffraction (XRD) patterns were recorded with a Philips PW1710 BASED Diffractometer, operating at 45 kV and 30 mA, fitted with a graphite monochromator getting Cu Kα 1 radiation (λ¼ 0.15406 nm). The samples were characterized by transmission electron microscopy (TEM), employing a Joel 100 CX2 (Tokyo, Japan) apparatus. Approximately one hundred palladium particles were measured to determine the particle size distribution to obtain the mean particle size (*d*).[17] Nitrogen adsorption/desorption isotherm at 77 K was obtained with a Nova 1200e Quantachrome Instrument. The specific surface areas were measured by following the Brunauer–Emmett–Teller (BET) method.

Synthesis of Pd Nanoparticles; General Procedure

Palladium catalyst supported on biochar (PdNPs/BC) was prepared by following the precipitation-reduction method, employing $PdCl_2$ as the metal precursor and biochar as the support.[18] BC was obtained as a product of the pyrolysis of lignocellulosic biomass.[12b]

Firstly, the BC was put in contact with a 10% nitric acid solution at r.t. for 2 h under stirring. The solid was extensively washed with deionized water. Afterwards, approximately 1 g of the sample was put in contact with a HCl aqueous solution of palladium chloride at 80 °C under stirring. A 37% formaldehyde solution and a 30% NaOH solution up to basic pH were added to attain palladium precipitation on support. Afterwards, the resulting solid was filtered and washed exhaustively with deionized water to remove the chloride. Finally, the catalyst was dried at 100 °C for 2 h and just before reaction it was calcined in air at 350 °C for 2 h.

One-Step Synthesis of Xanthones; General Procedure

Salicylaldehydes (1 mmol), 1,2-dihaloarenes (2 mmol), K_2CO_3 (2 mmol), PdNPs/BC (3 mol%), and anhydrous DMF (5 mL) were added to a vessel tube with a magnetic stirring bar. The resulting mixture was heated at 150 °C under microwave irradiation (250 W) for 30 min. The progress of the reaction was monitored by TLC and GC-MS. The crude product was treated with EtOAc. The catalyst was recovered by filtration and washed several times with the same solvent. The filtrate was washed twice with brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the desired xanthone was purified by column chromatography using silica gel 60 as adsorbent.

9*H*-Xanthen-9-one (3)

The product was obtained from salicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; hexane/EtOAc = 12:1). The spectral data were in accordance with those reported in the literature.[6g,j]

Yield: 0.17 g (0.88 mmol, 88%); white solid; mp 172–173 °C.

IR (film): 3070, 2914, 2874, 1654, 1456 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 6.0, 1.2 Hz, 2 H), 7.70–7.74 (m, 2 H), 7.48 (d, *J* = 6.4 Hz, 2 H), 7.35 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 156.1, 134.8, 126.7, 123.9, 121.8, 117.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_9O_2$: 197.0603; found: 197.0608.

2-Methyl-9*H*-xanthen-9-one (4)

The product was obtained from salicylaldehyde and 2-bromo-1-chloro-4-methylbenzene and purified by column chromatography (SiO_2; hexane/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[6g,j]

Yield: 0.17 g (0.82 mmol, 82%); white solid; mp 149–151 °C.

IR (film): 3062, 2915, 2871, 1657, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.0 Hz, 1 H), 8.04 (s, 1 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 7.27–7.32 (m, 2 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 155.2, 153.4, 135.0, 133.6, 132.7, 125.7, 125.0, 122.7, 120.8, 120.5, 116.9, 116.7, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}O_2$: 211.0759; found: 211.0764.

2-Bromo-9*H*-xanthen-9-one (5)

The product was obtained from salicylaldehyde and 1,2,4-tribromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 14:1). The spectral data were in accordance with those reported in the literature.[19]

Yield: 0.21 g (0.78 mmol, 78%); white solid; mp 176–178 °C.

IR (film): 3075, 2919, 1663, 1451 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.5 Hz, 1 H), 8.30 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.98–8.01 (m, 2 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.58–7.61 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 156.2, 155.1, 137.8, 135.5, 129.4, 127.0, 124.5, 123.3, 121.8, 120.2, 118.3, 117.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8BrO_2$: 274.9708; found: 274.9712.

The xanthone derivative **5** was also synthesized from 5-bromosalicylaldehyde and 1,2-dibromobenzene to give a white solid (0.17 g, 0.61 mmol, 61% yield).

2,3-Dimethoxy-9*H*-xanthen-9-one (6)

The product was obtained from salicylaldehyde and 1,2-dibromo-4,5-dimethoxybenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[6f,j]

Yield: 0.16 g (0.63 mmol, 63%); colorless oil.

IR (neat): 3065, 2940, 2834, 1648, 1466 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.0 Hz, 1 H), 7.63 (m, 1 H), 7.60 (s, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 6.85 (s, 1 H), 3.94 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 155.0, 154.4, 151.4, 145.7, 132.9, 125.5, 122.7, 120.5, 116.6, 113.9, 104.4, 98.6, 55.4, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}O_4$: 257.0814; found: 257.0819.

2-Nitro-9*H*-xanthen-9-one (7)

The product was obtained from salicylaldehyde and 1,2-dibromo-4-nitrobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 20:1). The spectral data were in accordance with those reported in the literature.[20]

Yield: 0.13 g (0.54 mmol, 54%); colorless solid; mp 153–154 °C.

IR (film): 3077, 1667, 1611, 1452 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.21–9.22 (m, 1 H), 8.85 (dd, *J* = 9.1, 2.8 Hz, 1 H), 8.40–8.42 (m, 1 H), 8.01–8.05 (m, 1 H), 7.98 (dd, *J* = 9.2, 0.3 Hz, 1 H), 7.75–7.77 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 159.5, 156.1, 136.1, 129.4, 127.2, 125.5, 123.8, 121.9, 121.6, 119.9, 118.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8NO_4$: 242.0453; found: 242.0459.

The xanthone derivative **7** was also synthesized from 5-nitrosalicylaldehyde and 1,2-dibromobenzene to give a colorless solid (0.16 g, 0.66 mmol, 66% yield).

2,3-Dimethyl-9*H*-xanthen-9-one (8)

The product was prepared from salicylaldehyde and 1,2-dibromo-4,5-dimethylbenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[6o]

Yield: 0.16 g (0.70 mmol, 70%); colorless oil; mp 151–153 °C.

IR (neat): 3062, 2955, 2851, 1654, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 7.9, 1.4 Hz, 1 H), 8.04 (s, 1 H), 7.67 (m, 1 H), 7.23–7.44 (m, 3 H), 2.39 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 156.3, 154.9, 145.7, 134.6, 133.3, 126.9, 126.5, 123.8, 122.1, 119.9, 118.3, 118.1, 20.8, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}O_2$: 225.0916; found: 225.0920.

3-Methoxy-9*H*-xanthen-9-one (9)

The product was obtained from 4-methoxysalicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.15 g (0.68 mmol, 68%); colorless solid; mp 112–114 °C.

IR (film): 3068, 2950, 2843, 1650, 1455 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 7.9 Hz, 1 H), 8.27 (d, *J* = 8.9 Hz, 1 H), 7.66–7.70 (m, 1 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 7.34–7.38 (m, 1 H), 6.93 (d, *J* = 8.9 Hz, 1 H), 6.86 (d, *J* = 2.3 Hz, 1 H), 3.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 165.3, 158.3, 156.4, 134.5, 128.5, 126.9, 124.2, 122.2, 117.9, 116.0, 113.5, 100.4, 56.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}O_3$: 227.0708; found: 227.0713.

4-Methoxy-9*H*-xanthen-9-one (10)

The product was obtained from 3-methoxysalicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 12:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.17 g (0.77 mmol, 77%); colorless solid; mp 110–112 °C.

IR (film): 3026, 2951, 2849, 1660, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.9 Hz, 1 H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.71–7.75 (m, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.22–7.31 (m, 2 H), 4.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 156.2, 148.8, 146.7, 135.1, 126.9, 124.3, 123.7, 122.9, 121.9, 118.5, 117.8, 115.5, 56.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}O_3$: 227.0708; found: 227.0712.

12*H*-benzo[*a*]xanthen-12-one (11)

The product was obtained from 2-hydroxy-1-naphthaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.18 g (0.72 mmol, 72%); white solid; mp 145–147 °C.

IR (film): 3073, 1663, 1600, 1455 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 9.2 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.65–7.74 (m, 2 H), 7.48–7.55 (m, 3 H), 7.39 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 156.6, 153.7, 135.7, 132.9, 130.2, 129.2, 128.56, 127.3, 125.9, 125.7, 125.1, 123.3, 122.6, 117.0, 116.5, 113.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{11}O_2$: 247.0759; found: 247.0764.

3-Hydroxy-9*H*-xanthen-9-one (12)

The product was obtained from 2,4-dihydroxybenzaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 2:1). The spectral data were in accordance with those reported in the literature.[21]

Yield: 0.13 g (0.60 mmol, 60%); white solid; mp 253–255 °C.

IR (KBr): 3455, 3073, 1667, 1601, 1452, 1120 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.15–8.17 (m, 1 H), 7.94 (d, *J* = 7.5 Hz, 1 H), 7.78 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.49–7.51 (m, 2 H), 6.99 (d, *J* = 1.4 Hz, 1 H), 6.94 (dd, *J* = 7.5, 1.4 Hz, 1 H), 2.44 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.5, 164.8, 158.9, 155.2, 134.5, 133.9, 128.2, 126.1, 123.9, 122.3, 118.7, 114.0, 103.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_9O_3$: 213.0552; found: 213.0557.

2-Chloro-9*H*-xanthen-9-one (13)

The product was prepared from 5-chlorosalicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 40:1). The spectral data were in accordance with those reported in the literature.[6o]

Yield: 0.20 g (0.86 mmol, 86%); white solid; mp 169–171 °C.

IR (film): 3078, 1662, 1602, 1460, 1316 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.30 (d, *J* = 2.6 Hz, 1 H), 7.75 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1 H), 7.67 (dd, *J* = 8.9, 2.6 Hz, 1 H), 7.44–7.52 (m, 2 H), 7.40 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 156.1, 154.5, 135.2, 134.9, 129.7, 126.8, 126.0, 124.3, 122.7, 121.5, 119.8, 118.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8ClO_2$: 231.0213; found: 230.0217.

4-(Diethylamino)-9*H*-xanthone (14)

The product was obtained from 4-(diethylamino)salicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 20:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.15 g (0.55 mmol, 55%); black oil.

IR (film): 3067, 2960, 2880, 1663, 1601, 1449 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.23 (m, 1 H), 8.05 (d, *J* = 9.2 Hz, 1 H), 7.52–7.56 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.19–7.25 (m, 1 H), 6.60–6.63 (m, 1 H), 3.35–3.41 (m, 4 H), 6.4 (s, 1 H), 1.17 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 157.6, 155.1, 151.8, 132.5, 127.1, 125.5, 122.3, 121.3, 116.3, 110.2, 108.4, 95.1, 43.8, 11.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_2$: 268.1338; found: 268.1343.

4-Methyl-9*H*-xanthen-9-one (15)

The product was obtained from 3-methylsalicylaldehyde and 1,2-dibromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 40:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.15 g (0.69 mmol, 69%); colorless solid; mp 125–127 °C.

IR (film): 3071, 2990, 1665, 1600, 1453 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.0 Hz, 1 H). 8.17 (d, *J* = 7.6 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 1 H), 7.70 (dd, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.36 (dd, *J* = 7.6, 7.0 Hz, 1 H), 7.25 (dd, *J* = 7.6, 7.0 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.8, 156.26, 154.7, 135.9, 134.9, 134.9, 127.5, 126.9, 124.5, 124.1, 123.6, 121.9, 121.8, 118.3, 16.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}O_2$: 211.0759; found: 211.0764.

2-Bromo-7-chloro-9*H*-xanthen-9-one (16)

The product was prepared from 5-chlorosalicylaldehyde and 1,2,4-tribromobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 10:1). The spectral data were in accordance with those reported in the literature.[22]

Yield: 0.19 g (0.63 mmol, 63%); white solid; mp 202–203 °C.

IR (KBr): 3071, 1665, 1603, 1455 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.44 (d, *J* = 2.4 Hz, 1 H), 8.28 (d, *J* = 2.6 Hz, 1 H), 7.82 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.69 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.6, 154.2, 152.9, 134.8, 132.7, 130.3, 128.8, 126.8, 121.6, 120.9, 120.1, 119.7, 114.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_7BrClO_2$: 308.9318; found: 308.9322.

2,7-Dimethyl-9*H*-xanthen-9-one (17)

The product was obtained from 5-methylsalicylaldehyde and 2-bromo-1-chloro-4-methylbenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 40:1). The spectral data were in accordance with those reported in the literature.[23]

Yield: 0.14 g (0.61 mmol, 61%); white solid; mp 128–130 °C.

IR (KBr): 3059, 1661, 1609, 1480 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.12 (dt, *J* = 1.4, 0.7 Hz, 2 H), 7.52 (ddd, *J* = 8.6, 2.3, 0.6 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 2.46 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.6, 152.9, 134.8, 132.7, 130.3, 128.8, 126.8, 121.6, 120.9, 120.1, 119.7, 114.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}O_2$: 225.0916; found: 225.0921.

2,7-Dibromo-9*H*-xanthen-9-one (18)

The product was obtained from 5-bromosalicylaldehyde and 1,2,4-tribromobezene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 25:1). The spectral data were in accordance with those reported in the literature.[23]

Yield: 0.19 g (0.54 mmol, 54%); white solid; mp 192–193 °C.

IR (KBr): 3059, 1660, 1608, 1458 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.43–8.42 (m, 2 H). 7.81 (ddd, *J* = 8.9 Hz, 2 H), 7.39 (dd, *J* = 8.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.9, 155.0, 138.2, 129.5, 122.9, 120.2, 117.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_7Br_2O_2$: 352.8813; found: 352.8817.

2,3-Dimethoxy-5-methyl-9*H*-xanthen-9-one (19)

The product was prepared from 3-methylsalcicylaldehyde and 1,2-dibromo-4,5-dimethoxybenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 15:1). The spectral data were in accordance with those reported in the literature.[6e]

Yield: 0.20 g (0.73 mmol, 73%); colorless oil.

IR (neat): 3075, 2945, 2860, 1666, 1601, 1454 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (d, *J* = 8.0 Hz, 1 H), 7.58 (s, 1 H), 7.44 (d, *J* = 7.4 Hz, 1 H), 7.16–7.20 (m, 1 H), 3.95 (s, 3 H), 6.86 (s, 1 H), 3.92 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.4, 154.4, 153.5, 151.3, 145.7, 133.8, 125.9, 123.1, 122.2, 120.3, 113.7, 104.4, 98.7, 55.5, 55.3, 14.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}O_4$: 271.0970; found: 271.0975.

2,7-Dinitro-9*H*-xanthen-9-one (20)

The product was prepared from 5-nitrosalicylaldehyde and 1,2-dibromo-4-nitrobenzene and purified by column chromatography (SiO_2; petroleum ether/EtOAc = 18:1). The spectral data were in accordance with those reported in the literature.[6c,24]

Yield: 0.18 g (0.64 mmol, 64%); yellow solid; mp 232–234 °C.

IR (KBr): 3058, 2917, 1667, 1605, 1531, 1463, 1345 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.07–9.12 (m, 2 H), 8.52–8.56 (m, 2 H), 7.65–7.69 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.3, 158.6, 144.5, 129.9, 123.3, 121.2, 120.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_6N_2O_6$: 286.0226; found: 286.0230.

Funding Information

This work was partially supported by the National Council of Scientific and Technical Research (Consejo Nacional de Investigaciones Científicas y Técnicas; CONICET), the National Agency for Scientific and Technological Promotion (Agencia Nacional de Promoción Científica y Tecnológica; ANPCyT), and the Universidad Nacional del Sur (Secretaría General de Ciencia y Tecnología, Universidad Nacional del Sur; SGCyT-UNS), Argentina. H.S.S. and P.M. thank CONICET and ANPCyT for a doctoral fellowship. D.C.G. is a research member of CONICET. Thanks are also given to ANPCyT for the purchase of the SPECS multitechnique analysis instrument (PME8-2003).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691069.

References and Notes

(1) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, **1984**, 3.
(2) (a) Masters, K. S.; Bräse, S. *Chem. Rev.* **2012**, *112*, 3717. (b) Vierira, L. M. M.; Kijjoa, A. *Curr. Med. Chem.* **2005**, *12*, 2413.
(3) (a) Sousa, E.; Pinto, M. M. *Curr. Med. Chem.* **2005**, *12*, 24472. (b) Suzuki, Y.; Fukuta, Y.; Ota, S.; Kamiya, M.; Sato, M. *J. Org. Chem.* **2011**, *76*, 3960. (c) Barbero, N.; SanMartin, R.; Domínguez, E. *Green Chem.* **2009**, *11*, 830. (d) Cardona, M. L.; Fernández, M. J.; Pedro, J. R.; Serrano, A. *Photochemistry* **1990**, *29*, 3003. (e) Woo, S.; Jung, J.; Lee, C.; Kwon, Y.; Na, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1163.
(4) (a) Menéndez, C. A.; Biscussi, B.; Accordino, R. S.; Murray, A. P.; Appignanesi, G. A.; Gerbino, D. C. *Bioorg. Chem.* **2017**, *75*, 201. (b) Shagufta, W.; Ahmad, I. *Eur. J. Med. Chem.* **2016**, *116*, 267.
(5) (a) Holleman, A. F. *Org. Synth.* **1927**, *7*, 84. (b) Blatt, A. H. *Org. React.* **1942**, *1*, 342. (c) Berlinger, E. *Org. React.* **1949**, *5*, 229. (d) Grover, P. K.; Shah, G. D.; Shah, R. C. *J. Chem. Soc.* **1955**, 3982. (e) Quillinan, A.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1329. (f) Jackson, W. T.; Robert, J. B.; Froelich, L. L.; Gapinski, D. M.; Mallett, B. E.; Sawyer, J. S. *J. Med. Chem.* **1993**, *36*, 1726. (g) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081. (h) Hassal, C. H.; Lewis, J. R. *J. Chem. Soc.* **1961**, 2312. (i) Murashige, R.; Hayashi, Y.; Ohmori, S.; Torii, A.; Aizu, Y.; Muto, Y.; Murai, Y.; Oda, Y.; Hashimoto, M. *Tetrahedron* **2011**, *67*, 641.
(6) For some recent synthetic xanthone routes, see: (a) Tang, J.; Zhao, S.; Wei, Y.; Quan, Z.; Huo, C. *Org. Biomol. Chem.* **2017**, *15*, 1589. (b) Venkanna, A.; Vinod, K.; Goud, P.; Prasad, P. V.; Shanker, M.; Rao, P. V. *ChemistrySelect* **2016**, *1*, 2271. (c) Rao, M. L. N.; Ramakrishna, B. S. *RSC Adv.* **2016**, *6*, 75505. (d) Shen, C.; Wu, X. F. *Synlett* **2016**, *27*, 1269. (e) Wang, S.; Xie, K.; Tan, Z.; An, X.; Zhou, X.; Guo, C. C.; Peng, Z. *Chem. Commun.* **2009**, *42*, 6469. (f) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (g) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (h) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928. (i) Yang, J.; Dong, C.; Li, H.; Li, Y. *Chin. Sci. Bull.* **2012**, *57*, 2364. (j) Wang, P.; Rao, H.; Hua, R.; Li, C. J. *Org. Lett.* **2012**, *14*, 902. (k) Manna, S. K.; Lavanya, S.; Manda, K.; Panda, G. *Tetrahedron Lett.* **2014**, *55*, 5759. (l) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5204. (m) Xu, Y.; Zhou, J.; Zhang, C.; Chen, K.; Zhang, T.; Du, Z. *Tetrahedron Lett.* **2014**, *55*, 6432. (n) Genovese, S.; Fiorito, S.; Specchiulli, M. C.; Taddeo, V. A.; Epifano, F. *Tetrahedron Lett.* **2015**, *56*, 847. (o) Hu, J.; Adogla, E. A.; Ju, Y.; Fan, D.; Wang, Q. *Chem. Commun.* **2012**, *48*, 11256. (p) Rao, H.; Ma, X.; Liu, Q.; Li, Z.; Cao, S.; Li, C. J. *Adv. Synth. Catal.* **2013**, 355. (q) Suzuki, Y.; Fukuta, Y.; Ota, S.; Kamiya, M.; Sato, M. *J. Org. Chem.* **2011**, *76*, 3960. (r) Jiang, N.; Li, S. Y.; Xie, S. S.; Yao, H.; Sun, H.; Wang, X. B.; Kong, L. Y. *RSC Adv.* **2014**, *4*, 63632. (s) Barbero, N.; San Martin, R.; Domínguez, E. *Green Chem.* **2009**, *11*, 830. (t) Hintermann, L.; Masuo, R.; Suzuki, K. *Org. Lett.* **2008**, *10*, 4859. (u) Woydziak, Z. R.; Fu, L.; Peterson, B. R. *J. Org. Chem.* **2012**, *77*, 473. (v) Johnson, M. M.; Naidoo, J. M.; Fernandes, M. A.; Mmutlane, E. M.; van Otterlo, W. A.; de Koning, B. A. *J. Org. Chem.* **2010**, *75*, 8701.
(7) (a) Hemalatha, K.; Madhumitha, G.; Kajbafvala, A.; Anupama, N.; Sompalle, R.; Roopan, M. S. *J. Nanomater.* **2013**, 341015. (b) Polshettiwar, R.; Varma, S. *Green Chem.* **2010**, *12*, 743. (c) Astruc, D. *Nanoparticles and Catalysis*; Wiley-VCH: Weinheim, **2008**, Chap. 1.
(8) (a) Sosnik, A.; Gotelli, G.; Abraham, G. A. *Prog. Polym. Sci.* **2011**, *36*, 1050. (b) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127.
(9) Atwood, D. A. *Sustainable Inorganic Chemistry*; Wiley-VCH: Weinheim, **2016**, 333.
(10) (a) Menéndez, C. A. *Doctoral Dissertation*; Universidad Nacional del Sur: Argentina, **2018**. (b) Scoccia, J.; Castro, M. J.; Faraoni, M. A.; Bouzat, C.; Martín, V. S.; Gerbino, D. C. *Tetrahedron* **2017**, *73*, 2913. (c) Menéndez, C.; Nador, F.; Radivoy, G.; Gerbino, D. C.

Org. Lett. **2014**, *16*, 2846. (d) Sierra, M. B.; Alarcón, L.; Gerbino, D. C.; Pedroni, V. I.; Buffo, F. E.; Morini, M. A. *Chem. Phys. Lipids* **2017**, 206.

(11) (a) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510. (b) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823. (c) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (d) Solé, D.; Mariani, F. *J. Org. Chem.* **2013**, *78*, 8136. (e) Nowrouzi, N.; Motevalli, S.; Tarokh, D. *J. Mol. Catal. A: Chem.* **2015**, *396*, 224. (f) Solé, D.; Mariani, F.; Fernández, I. *Eur. J. Org. Chem.* **2015**, 3935.

(12) (a) Casoni, A. I.; Bidegain, M.; Cubitto, M.; Curvetto, N.; Volpe, M. *Bioresour. Technol.* **2014**, *177*, 406. (b) Casoni, A. I.; Hoch, P. M.; Volpe, M.; Gutierrez, V. J. *J. Cleaner Prod.* **2018**, *178*, 237.

(13) For a very interesting review on transition-metal-catalyzed site-selective cross-coupling reactions of di- and polyhalogenated compounds, see: Wang, J. R.; Manabe, K. *Synthesis* **2009**, 1405.

(14) (a) Solé, D.; Mariani, F. *J. Org. Chem.* **2013**, *78*, 8136. (b) Tsuda, T.; Satoh, T.; Miura, M. *Chem. Lett.* **1997**, 1103. (c) Satoh, T.; Inoh, J. C.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (d) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (e) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961.

(15) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.

(16) Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, **1988**.

(17) Schölten, J. F.; Pijpers, A. P.; Hustings, M. L. *Catal. Rev.: Sci. Eng.* **1985**, *27*, 151.

(18) Mozingo, R. *Org. Synth.* **1955**, *3*, 685.

(19) Gardikis, Y.; Tsoungas, P. G.; Potamitis, C.; Zervou, M.; Cordopatis, P. *Heterocycles* **2011**, *83*, 1077.

(20) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

(21) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075.

(22) Fremeau, T.; White, R. D. Jr.; Patel, V. F. *J. Med. Chem.* **2014**, *57*, 9796.

(23) Granoth, I.; Pownall, H. J. *J. Org. Chem.* **1975**, *40*, 2088.

(24) Dhar, S. N. *J. Chem. Soc., Trans.* **1920**, *117*, 1053.

