Efficient Preparation of Methyl 2-Oxo-3-aryl (heteroaryl)-2*H*-pyran-5-carboxylate via Pd-Catalyzed Negishi Coupling

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Methyl 3-bromocoumalate, readily obtained from methyl 2-pyrone-5-carboxylate (methyl coumalate), is easily substituted by cross-coupling reactions with arylzinc reagents under palladium catalysis, leading to methyl 2-oxo-3-aryl (heteroaryl)-2H-pyran-5-carboxylates.

Introduction

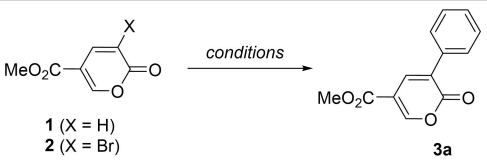
Natural products[1–3] containing a pyran-2-one core are widespread in microbials, bacteria, fungi,[4] plant, alga, animal sources and are characterized by remarkably diverse bioactivities ranging from sex pheromone,[5] anti-bacterial,[6] antifungal,[7] cardioactive, cytotoxic,[8] insecticidal,[9] neuroprotective and anti-cancer activities.[10] In the framework of a project aiming biomass valorization we got interested in **methyl 2-pyrone-5-carboxylate** (methyl coumalate, MC),[11] a renewable feedstock ultimately accessible from malic acid[12] that holds a significant role as aromatic ring precursor.[13–19] MC can be considered as a good molecular platform candidate as this ambivalent compound possesses an extrinsic reactivity that depends on its reaction partners.[20] Therefore, beside involvement in cycloaddition reaction,[21–25] another feature related to the electron deficient conjugated diene moiety is its propensity to undergo 1,6 addition reactions with organometallic reagents followed by an opening electrocyclic reaction to give functionalized β,γ unsaturated carboxylic acids,[26] or α,γ dienoic acids.[27] In addition, reactions with soft nucleophiles such as β-ketoesters, 1,3-diketones, or amines allow access to *2H*-pyrans,[28] aromatic compounds,[29] and pyridines,[30–31] respectively. To the best of our knowledge, the involvement of methyl coumalate in a cross-vinylogous Rauhut-Currier reaction[32] and in a Morita-Baylis-Hillman reaction[33] are the scarce examples of processes giving access to coumalate adducts. Surprisingly, there is no report of carbon-carbon bond formation from methyl 3-bromo coumalate (3-BrMC) and an organometallic species under transition metal catalysis, whereas brominated, triflyloxy- or tosyloxy-pyran-2-ones readily react under Sonogashira,[34] Negishi,[5] Suzuki,[35–38] Stille[39–42]–type couplings or with Me_3Al – dimethylaminoethanol complex as coupling reagent.[43] The reason may lie on the high reactivity of the more electron-depleted coumalate ring towards nucleophilic species which disrupts the coupling reaction. Therefore, synthetic methods allowing to maintain the pyrone unit remain of high consideration to prospect new bioactive products with simpler structures[44–45] or synthetic intermediates for further transformations.[46]

Thus, we wish to disclose herein an efficient and mild method to prepare 3-arylcoumalates, a new family of biobased molecules, through Pd-catalyzed Negishi cross-coupling reactions of methyl 3-bromocoumalate and functionalized arylzinc species.

Results and Discussion

This work was initialized by examining whether classical methods developed in our laboratory could be appropriate for the arylation of either MC or methyl 3-bromocoumalate (3-BrMC). This latter could be easily obtained from MC using bromine and triethylamine.[47] It first appeared that the electrochemical conjugate addition[48,49] of bromobenzene onto MC as Michael acceptor to get 1,4 and/or 1,6 addition products is not appropriate for MC as substrate (Table 1, entry 1). Similarly, electrochemical coupling of 3-BrMC with bromobenzene to get

Table 1. Initial findings.



1 (X = H)
2 (X = Br)

3a

Entry	Substrate	Reagent	Conditions	Yield [%][a]
1	1 (2.5 equiv.)	PhBr (1.0 equiv.)	$NiBr_2.xH_2O$ (5 mol%), e-, iron rod, NBu_4Br, DMF/pyridine or DMF/acetonitrile, 70 °C	–[b]
2	2	PhBr (1.0 equiv)	$NiBr_2$.bpy (5 mol%), e^-, aluminum or zinc rod, NBu_4Br, DMF, rt	–[b]
3	2	Ph_3Bi (0.33 equiv)	PEPPSI IPr (5 mol%), PPh_3 (10 mol%), CsF (3.0 equiv.) DMF, 90 °C, 14 h	–[b]
4	2	PhZnBr (1.5 equiv)	$PdCl_2(PPh_3)_2$ (0.5 mol%), DMF/ Acetonitrile, 50 °C, 14 h	32

[a] Isolated yield. [b] Substrate degradation.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100608

biaryl derivatives[50] such **3** failed (Table 1, entry 2). Thus, we definitively turned our attention to chemical methods involving cross-coupling reaction of 3-BrMC with organometallic species under palladium catalysis. First the stability of 3-BrMC and methyl 3-phenylcoumalate have been evaluated in toluene in the presence of K_2CO_3 or *t*-BuOK (2 equiv.). Degradation of both products, ranging from 50% to 100%, was observed after 3 hours at 120 °C or even at room temperature, although more slowly. For these reasons, we did not investigate further the Suzuki cross-coupling strategy.

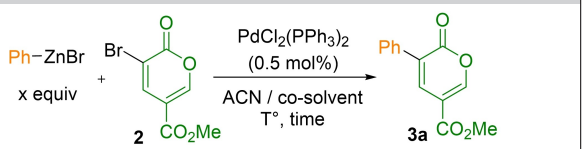
If the use of triphenylbismuth[51] (Table 1, entry 3), a soft organometallic species,[52] led to a degradation of the starting material, the use of phenylzinc bromide, prepared according to Gosmini's method,[53] with a simple $PdCl_2(PPh_3)_2$ precatalyst delivered the expected product **3** in a promising 32% yield (Table 1, entry 4). Thus, this initial hit prompted us to carry out the optimization of the reaction conditions with phenylzinc bromide as the nucleophilic partner. Results are reported in Table 2.

As a preamble, it is important to keep in mind that organozinc reagents were prepared by activation of the corresponding aryl bromide under a cobalt catalysis in acetonitrile (ACN) in the presence of an excess of Zn° dust (3 equiv.) prior to cross-coupling. In a previous study, it was found that DMF as co-solvent of ACN could advantageously enhance the efficiency of Negishi cross-coupling reactions.[54] Therefore, at this stage, we decided to perform this study under this solvent combination. In a first series of experiments, we tried to determine whether the organozinc reagent could be used in the presence of remaining zinc dust or if a decantation was necessary to remove this reducing metal. Thus, whereas the addition of 3-BrMC and $PdCl_2(PPh_3)_2$ as a catalyst to a freshly prepared heterogeneous solution of organozinc reagent led to the decomposition of methyl 3-bromocoumalate **2** and formation of biphenyl (entry 1), the coupling product was obtained in satisfactory yield after removal of the unreacted zinc dust (entry 2), hence indicating chemical incompatibility between Zn(0) and catalyst and/or 3-BrMC **2**. It can be noted that no coupling product was detected by GC in the absence of $PdCl_2(PPh_3)_2$, thus indicating that the remaining traces of cobalt salts in the organozinc solution did not catalyze the coupling reaction (entry 3). The corresponding Ni-based pre-catalyst was assessed instead of $PdCl_2(PPh_3)_2$, but these conditions failed to deliver the expected product (entry 4). We observed that a more important amount of the arylzinc species (1.5 equiv.) is beneficial to the reaction (entries 2 and 5) whereas longer reaction times resulted in decreased yields, indicating a probable instability of the coupling product under the reaction conditions (entry 6). Therefore, the reaction temperature was logically lowered from 50 °C to room temperature (entry 7), resulting in improved yields, even with only 1.2 equiv. of the arylzinc compound (entry 8). However, only partial conversion of the starting material occurred at 0 °C (entry 9). Other solvents combinations like ACN/THF (entry 10) or pure ACN (entry 11) also gave significant results, thus demonstrating the robustness of these conditions.

The scope of the reaction was then explored with various substituted arylzinc reagents easily reached and bearing electro-withdrawing or -donating groups under ACN or ACN/DMF combination. The best results are reported in Table 3.

Thus, the optimized reaction conditions could be applied to a variety of substituted arylzinc reagents and isolated yields are generally high (>75% in most cases). The introduction of electron-withdrawing groups such as a fluorine (99%, entry 2), a trifluoromethyl (79%, entry 3) or an ester group (85–92%, entry 4–5) is well-tolerated in the *para* position and is also possible in the *meta* position as illustrated by the use of ketone derivative (92%, entry 6). However, no reaction was observed with the organozinc species prepared from 4-bromobenzonitrile, probably due to catalyst poisoning. In the case of electron-donating groups, yields were slightly lower as 83% and 82% yield were obtained with a methyl (entry 7) or a methoxy group (entry 8), respectively. Moreover, the study of the methoxy

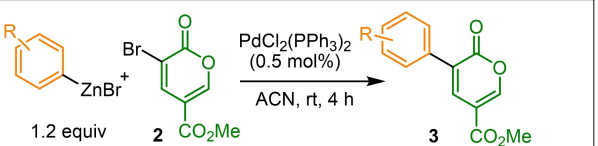
Table 2. Optimization of the reaction conditions.



Entry[a]	x	Co-Solvent	T [°C]	Time [h]	Yield [%][b]
1	excess[c]	DMF	rt	4	–[d]
2	1.0	DMF	50	4	53
3	1.0	DMF	50	4	–[e]
4[f]	1.5	DMF	20	4	–[e]
5	1.5	DMF	50	4	65
6	1.5	DMF	50	18	32
7	1.5	DMF	rt	4	74
8	1.2	DMF	rt	4	70
9	1.2	DMF	0	4	–[g]
10	1.2	THF	rt	4	84
11	1.2	–	rt	4	91

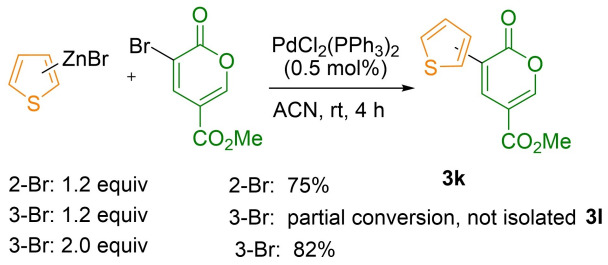
[a] Reaction conditions: 3-BrMC: 1 mmol, co-solvent (1 M). [b] Isolated yield. [c] No filtration of the organozinc solution made from PhBr (10.0 mmol), leading to PhZnBr: 14.0 mL, 0.43 M. [d] Substrate degradation. [e] No reaction. [f] $NiBr_2(PPh_3)_2$ 0,5% was tested as catalyst. [g] Partial conversion. The product was not isolated.

Table 3. Scope of arylzinc reagents.[a]



Entry	R	Product	Yield [%][b]
1	H	**3a**	91
2	*p*-F	**3b**	99
3	*p*-CF_3	**3c**	79[c]
4	*p*-CO_2Me	**3d**	85[c]
5	*p*-CO_2Et	**3e**	92
6	*m*-$COCH_3$	**3f**	92
7	*p*-CH_3	**3g**	83[c]
8	*p*-OMe	**3h**	82[c]
9	*m*-OMe	**3i**	88[c]
10	*o*-OMe	**3j**	51[c]

[a] Reaction conditions: 3-BrMC: 1–5 mmol. [b] Isolated yield. [c] Use of a co-solvent: DMF (1 M).



Scheme 1. Optimization in the preparation of thienyl adducts.

derivatives (entries 8–10) revealed not only the influence of the electronics factors (improved 88% yield with a *meta* substitution) but also of the steric effects as only 51% yield was obtained with the ortho-substituted organozinc reagent (entry 10).

To expand the usefulness of this methodology, we also examined the cross-coupling reactions of 2 and 3-thienylzinc bromide with 3-BrMC (Scheme 1). Whereas a good yield (75%) was obtained with 2-thienylzinc bromide under ACN as sole solvent, the cross-coupling reaction with 3-thienylzinc bromide was less efficient and only gave a partial conversion of 3-BrMC (Scheme 1). However, a significant improvement was obtained by conducting the reaction with a higher excess of the organozinc reagent (2 equiv.).

Conclusion

In summary, we have disclosed an unprecedented access to methyl 3-aryl- and 3-heteroaryl-coumalates. The reaction, which is characterized by its simplicity, allows the efficient coupling of arylzinc compounds and methyl 3-bromocoumalate at room temperature with only low amounts of a simple palladium pre-catalyst. Valorization of these new readily available products through their involvement in post-transformation reactions is underway and will be reported in due course.

Experimental Section

General Information. All commercially available reagents were used as received. Solvents (Acetonitrile = ACN, DMF, THF, ethyl acetate = EA, petroleum ether = PE, cyclohexane = Cy, CCl_4, dichloromethane = DCM) were used as received. Room temperature means 18–25 °C. Melting points (mp) are uncorrected and were measured on a Büchi B-545 apparatus. Analytical thin layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator (Merck 60F254). Visualization was effected using ultraviolet light (l = 254 nm) and/or a aqueous solution of $KMnO_4$. Flash chromatography (FC) was performed on 40–63 μm silica gel with mixtures of solvents. Gas chromatography (GC) was recorded on a Shimadzu 2025 chromatograph ($T_{inj} = T_{det} = 250$ °C) with a ZB-5MSi capillary column (l = 5,5 m), using nitrogen as carrier gas and a flame-ionization detector. Retention times are given in minutes (min). High-Resolution Mass Spectra were obtained at the ICOA of the Université d'Orléans by electrospray ionization using a Q-TOF analyzer. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer. ^{1}H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). Data are presented as follows: chemical shift δ (ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *quint* = quintet, *hept* = heptuplet, *m* = multiplet, *br* = broad), coupling constant *J* (Hz), integration.

Preparation of methyl 3-bromocoumalate (3-BrMC)

Compound 2.[42] A 500 mL RBF equipped with a stir bar was charged with methyl coumalate (7.706 g, 50.0 mmol, 1 equiv) and CCl_4 (100 mL, 0.5 M). A solution of bromine (5.6 mL, 115 mmol, 2.3 equiv) in CCl_4 (40 mL) was added dropwise to the stirred mixture with a pressure-equalizing dropping funnel at rt. Then, the RBF was equipped with a reflux condenser and the reaction was heated at reflux for 4 h. After cooling to rt, the excess of bromine was removed by bubbling argon (or air) in the reaction for 10 min. The mixture was cooled to 0 °C (ice/water bath) and Et_3N (16.0 mL, 115 mmol, 2.3 equiv) was added dropwise with a pressure-equalizing dropping funnel. The reaction was then allowed to warm to rt and stirred for 1 h. After addition of 50 mL of DCM, the resulting mixture was washed with water (3*100 mL) and NaCl sat (100 mL), dried over Na_2SO_4, and evaporated. The desired product was obtained after purification by FC [$V(SiO_2)$ = 200 mL, PE/DCM: 40/60 (1000 mL), 30/70 (1000 mL)] as a beige solid (5.858 g, 49%). mp: 133–134 °C (litt: 131–134 °C). R_f (DCM, UV + $KMnO_4$): 0.51. GC (50 + 10/250–5): 11.2 min. HRMS (ESI$^+$): $[M+H]^+$ Calcd. for $C_7H_6BrO_4$: 232.9444. Found: 232.9444. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.14 (s, 1H), 3.87 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.5 (C), 156.8 (C), 156.6 (CH), 142.7 (CH), 112.8 (C), 111.6 (C), 52.9 (CH_3).

Preparation of methyl 3-arylcoumalates

General procedure 1 (GP1): Step 1. A 50 mL RBF equipped with a stir bar, closed with a septum and purged with Ar, was charged with Zn (3.0 equiv) and ACN (C = 0.7 M). Trifluoroacetic acid (15 mol%) and 1,2-dibromoethane (20 mol%)[55] were added with syringes and the suspension was stirred and heated to reflux with a heat gun. After cooling to rt, the (hetero)aryl bromide (*y* mmol) and $CoBr_2$ (10 mol%) were added and the reaction was stirred at rt for 1 h. The excess of zinc was decanted and the solution of organozinc reagent was titrated by reaction with I_2. *Step 2*. A 50 mL RBF equipped with a stir bar, closed with a septum and purged with Ar, was charged with methyl 2-bromocoumalate (*x* mmol), $PdCl_2(PPh_3)_2$ (0.05 mol%) closed with a septum and purged with Ar. The decanted solution of organozinc reagent in ACN (*v* mL, *c* M, 1.2 equiv), and in some cases DMF (C = 1 M) were successively added and the reaction was stirred at rt for 4 h. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the resulting solution was extracted with EA (2*50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and evaporated. Purification by FC afforded the expected product.

Compound 3a. Following GP1, the reaction performed with bromobenzene (1.1 mL, 10.0 mmol) afforded the corresponding organozinc reagent (2.3 mL, C = 0.53 M) and after reaction with methyl 2-bromocoumalate (235 mg, 1.0 mmol) and $PdCl_2(PPh_3)_2$ (3.5 mg, 5 μmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [$V(SiO_2)$ = 50 mL, PE/EA: 80/20 (600 mL)] as a yellow solid (211 mg, 91%). mp: 90–92 °C. R_f (PE/EA: 90/10, UV + $KMnO_4$): 0.21. GC (50 + 10/250–5): 16.1 min. HRMS (ESI$^+$): $[M+H]^+$ Calcd. for $C_{13}H_{11}O_4$: 231.0652. Found: 231.0652. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.92 (s, 1H), 7.67 (d, *J* = 8.0 Hz,

2H), 7.48–7.37 (m, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7 (C), 160.1 (C), 156.6 (CH), 137.7 (CH), 133.8 (C), 129.3 (CH), 128.6 (2 CH), 128.3 (2 CH), 127.2 (C), 112.7 (C), 52.6 (CH_3).

Compound 3b. Following GP1, the reaction performed with 1-bromo-4-fluorobenzene (1.6 mL, 15.0 mmol) afforded the corresponding organozinc reagent (12.8 mL, C = 0.47 M) and after reaction with methyl 2-bromocoumalate (1.175 g, 5.0 mmol) and $PdCl_2(PPh_3)_2$ (18.0 mg, 25 μmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, PE/EA: 80/20 (500 mL), 70/30 (500 mL)] as a yellow solid (1.284 g, quantitative). mp: 121–123 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.36. GC (50 + 10/250-5): 15.9 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{13}H_{10}FO_4$: 249.0557. Found: 249.0560. ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.89 (s, 1H), 7.70 –7.62 (m, 2H), 7.11 (t, J = 8.6 Hz, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6 (d, $^1J_{C\text{-}F}$ = 248.3 Hz, CF), 162.3 (C), 160.0 (C), 156.6 (CH), 137.5 (CH), 130.3 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, 2 CH), 129.8 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C), 126.2 (C), 115.7 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, 2 CH), 112.7 (C), 52.7 (CH_3). $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$): −111.7 (s, 1 F).

Compound 3c. Following GP1, the reaction performed with 1-bromo-4-(trifluoromethyl)benzene (1.4 mL, 10.0 mmol) afforded the corresponding organozinc reagent (4.6 mL, C = 0.52 M) and after reaction with methyl 2-bromocoumalate (470 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 5 μmol, 0.5 mol%) in DMF (2 mL), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 50 mL, PE/EA: 80/20 (500 mL), 70/30 (100 mL)] as a pale yellow solid (474 mg, 79%). mp: 134–135 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.34. GC (150 + 10/250–10): 6.0 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{14}H_{10}F_3O_4$: 299.0525. Found: 299.0523. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5 (C), 159.6 (C), 157.4 (CH), 138.9 (CH), 137.3 (C), 131.2 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C), 128.7 (2 CH), 125.9 (C), 125.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, 2 CH), 124.0 (q, $^1J_{C\text{-}F}$ = 272.5 Hz, CF_3), 112.7 (C), 52.8 (CH_3). $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$): −62.8 (s, 3 F).

Compound 3d. Following GP1, the reaction performed with methyl 4-bromobenzoate (2.150 g, 10.0 mmol) afforded the corresponding organozinc reagent (5.5 mL, C = 0.44 M) and after reaction with methyl 2-bromocoumalate (470 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 5 μmol, 0.5 mol%) in DMF (2 mL), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 50 mL, PE/EA: 70/30 (500 mL), 60/40 (400 mL), 40/60 (200 mL)] as a pale yellow solid (491 mg, 85%). mp: 138 °C (decomposition). R_f (PE/EA: 70/30, UV + $KMnO_4$): 0.33. GC (50 + 10/250–5): 20.2 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{15}H_{13}O_6$: 289.0706. Found: 289.0705. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 2.2 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 163.5 (C), 159.6 (C), 157.3 (CH), 138.8 (CH), 138.1 (C), 130.7 (C), 129.9 (2 CH), 128.3 (2 CH), 126.2 (C), 112.7 (C), 52.8 (CH_3), 52.4 (CH_3).

Compound 3e. Following GP1, the reaction performed with ethyl 4-bromobenzoate (2.4 mL, 15.0 mmol) afforded the corresponding organozinc reagent (12.0 mL, C = 0.45 M) and after reaction with methyl 2-bromocoumalate (1.057 g, 4.5 mmol) and $PdCl_2(PPh_3)_2$ (16.0 mg, 23 μmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, PE/EA: 70/30 (500 mL), 50/50 (400 mL)] as a yellow solid (1.260 g, 92%). mp: 96–98 °C. R_f (PE/EA: 70/30, UV + $KMnO_4$): 0.47. GC (50 + 10/250–5): 20.7 min.

HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{16}H_{15}O_6$: 303.0863. Found: 303.0862. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.6 Hz, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 2.6 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 166.2 (C), 163.5 (C), 159.6 (C), 157.2 (CH), 138.7 (CH), 138.0 (C), 131.0 (C), 129.8 (2 CH), 128.3 (2 CH), 126.2 (C), 112.7 (C), 61.3 (CH_2), 52.7 (CH_3), 14.4 (CH_3).

Compound 3f. Following GP1, the reaction performed with methyl 4′-bromoacetophenone (2.0 mL, 15.0 mmol) afforded the corresponding organozinc reagent (12.5 mL, C = 0.42 M) and after reaction with methyl 2-bromocoumalate (1.058 g, 4.5 mmol) and $PdCl_2(PPh_3)_2$ (16 mg, 23 μmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, PE/EA: 70/30 (500 mL), 60/40 (500 mL)] as a yellow solid (1.127 g, 92%). mp: 105–108 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.13. GC (50 + 10/250–5): 19.6 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{15}H_{13}O_5$: 273.0757. Found: 273.0757. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.22 (s, 1H), 7.99–7.94 (m, 2H), 7.88 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 3.89 (s, 3H), 2.62 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.7 (C), 163.5 (C), 159.9 (C), 157.0 (CH), 138.4 (CH), 137.4 (C), 134.3 (C), 132.9 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 126.2 (C), 112.7 (C), 52.7 (CH_3), 26.8 (CH_3).

Compound 3g. Following GP1, the reaction performed with 4-bromotoluene (1.2 mL, 10.0 mmol) afforded the corresponding organozinc reagent (5.5 mL, C = 0.44 M) and after reaction with methyl 2-bromocoumalate (470 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 5 μmol, 0.5 mol%) in DMF (2 mL), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 50 mL, PE/EA: 90/10 (250 mL), 80/20 (250 mL), 70/30 (100 mL)] as a yellow solid (410 mg, 83%). mp: 69–72 °C. R_f (PE/EA: 90/10, UV + $KMnO_4$): 0.27. GC (50 + 10/250–5): 17.2 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{14}H_{12}O_4$: 245.0808. Found: 245.0806. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 3.89 (s, 3H), 2.38 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8 (C), 160.2 (C), 156.2 (CH), 139.4 (C), 137.0 (CH), 130.9 (C), 129.3 (2 CH), 128.2 (2 CH), 127.1 (C), 112.7 (C), 52.6 (CH_3), 21.4 (CH_3).

Compound 3h. Following GP1, the reaction performed with 4-bromoanisole (1.3 mL, 10.0 mmol) afforded the corresponding organozinc reagent (4.8 mL, C = 0.50 M) and after reaction with methyl 2-bromocoumalate (470 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 5 μmol, 0.5 mol%) in DMF (2 mL), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 50 mL, PE/EA: 90/10 (250 mL), 80/20 (250 mL), 70/30 (100 mL)] as a yellow solid (431 mg, 82%). mp: 115–118 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.39.

GC (150 + 10/250–5): 8.8 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{14}H_{13}O_5$: 261.0757. Found: 261.0757. ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9 (C), 160.5 (C), 160.3 (C), 155.9 (CH), 136.3 (CH), 129.7 (2 CH), 126.8 (C), 126.1(C), 114.1 (2 CH), 112.7 (C), 55.5 (CH_3), 52.6 (CH_3).

Compound 3i. Following GP1, the reaction performed with 3-bromoanisole (1.3 mL, 10.0 mmol) afforded the corresponding organozinc reagent (5.3 mL, C = 0.45 M) and after reaction with methyl 2-bromocoumalate (470 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 5 μmol, 0.5 mol%) in DMF (2 mL), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 50 mL, PE/EA: 80/20 (250 mL), 70/30 (250 mL)] as a yellow solid (461 mg, 88%). mp: 64–66 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.34. GC (150 + 10/250–10): 8.4 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{14}H_{13}O_5$: 261.0757. Found: 261.0758. ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.25–7.21 (m, 2H), 6.94 (d, J = 8.2 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7 (C), 159.9 (C), 159.7 (C), 156.6

(CH), 137.9 (CH), 135.1 (C), 129.7 (CH), 127.0 (C), 120.7 (CH), 115.0 (CH), 113.9 (CH), 112.6 (C), 55.5 (CH_3), 52.6 (CH_3).

Compound 3j. Following GP1, the reaction performed with 2-bromoanisole (1.9 mL, 15.0 mmol) afforded the corresponding organozinc reagent (11.3 mL, C = 0.53 M) and after reaction with methyl 2-bromocoumalate (1.175 g, 5.0 mmol) and $PdCl_2(PPh_3)_2$ (18.0 mg, 25 µmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, DCM/PE: 80/20 (500 mL), 90/10 (500 mL), 100/0 (400 mL)] as a yellow solid (665 mg, 51%). mp: 78–81 °C. R_f (DCM, UV + $KMnO_4$): 0.34. GC (50 + 10/250–5): 17.4 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{14}H_{13}O_5$: 261.0757. Found: 261.0757. ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.82 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.04–6.94 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8 (C), 159.7 (C), 157.1 (C), 156.8 (CH), 139.8 (CH), 130.7 (CH), 130.6 (CH), 125.6 (C), 123.3 (C), 120.7 (CH), 112.3 (C), 111.4 (CH), 55.8 (CH_3), 52.5 (CH_3).

Compound 3k. Following GP1, the reaction performed with methyl 2-bromothiophene (0.96 mL, 10.0 mmol) afforded the corresponding organozinc reagent (10.0 mL, C = 0.50 M) and after reaction with methyl 2-bromocoumalate (987 mg, 4.2 mmol) and $PdCl_2(PPh_3)_2$ (15 mg, 21 µmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, PE/EA: 90/10 (500 mL), 70/30 (500 mL)] as a yellow solid (753 mg, 75%). mp: 109–110 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.30. GC (50 + 10/250–5): 16.5 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{11}H_9O_4S$: 237.0216. Found: 237.0217. ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 2.3 Hz, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 7.76 (d, *J* = 3.7 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.14–7.07 (m, 1H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 159.0 (C), 155.0 (CH), 135.1 (C), 133.3 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 121.3 (C), 112.7 (C), 52.7 (CH_3).

Compound 3l. Following GP1, the reaction performed with methyl 3-bromothiophene (1.4 mL, 15.0 mmol) afforded the corresponding organozinc reagent (16.0 mL, C = 0.50 M, 2.0 equiv) and after reaction with methyl 2-bromocoumalate (940 mg, 4.0 mmol) and $PdCl_2(PPh_3)_2$ (14 mg, 20 µmol, 0.5 mol%), the desired product was obtained after purification by flash chromatography [V(SiO_2) = 100 mL, PE/EA: 80/20 (500 mL), 70/30 (500 mL)] as a yellow solid (776 mg, 82%). mp: 110–112 °C. R_f (PE/EA: 80/20, UV + $KMnO_4$): 0.39. GC (50 + 10/250–5): 16.4 min. HRMS (ESI^+): $[M+H]^+$ Calcd. for $C_{11}H_9O_4S$: 237.0216. Found: 237.0218. ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 3.0, 1.3 Hz, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.37 (dd, *J* = 5.1, 3.0 Hz, 1H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8 (C), 159.5 (C), 155.4 (CH), 134.9 (CH), 133.5 (CH), 126.4 (CH), 126.1 (CH), 126.0 (CH), 121.8 (C), 112.5 (C), 52.6 (CH_3).

Acknowledgements

The financial support of this work by the CNRS, the University Paris-Est Créteil and the University Paris-Est (PhD grant to T. Xavier) is gratefully acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–C Coupling · Coumalate · Palladium · Zinc

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[55] Please note the short modification done concerning the method described by C. Gosmini: allyl chloride was replaced by 1,2 dibromoethane for the activation of the zinc dust.

Manuscript received: May 19, 2021
Revised manuscript received: June 21, 2021
Accepted manuscript online: June 28, 2021

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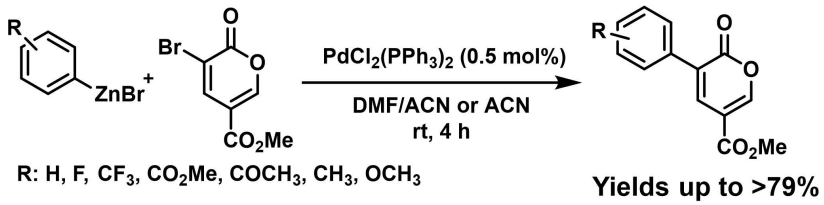

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A Negishi type coupling is reported allowing access to methyl 3-aryl (heteroaryl) coumalates. The synthesis of methyl coumalate adducts is characterized by a low catalyst loading, high functional tolerance, and high yields.