







Article

Efficient Synthesis of Fluorescent Coumarins and Phosphorous-Containing Coumarin-Type Heterocycles via Palladium Catalyzed Cross-Coupling Reactions

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Abstract: Quantum-chemical calculations on the spectral properties of some aryl substituted 3-phosphonocoumarins were performed, and the effect of the substituents in the aryl moiety was evaluated. The structures possessing promising fluorescent properties were successfully synthesized via Suzuki and Sonogashira cross-coupling. The synthetic protocol was also applied for the phosphorous chemoisomer of 3-phosphonocoumarin, 1,2-benzoxaphosphorin, and their carboxylate analogues. The optical properties of the arylated and alkynylated products were experimentally determined. The obtained quantum-chemical and experimental results give the possibility for a fine tuning of the optical properties of phosphorous-containing coumarin systems by altering the substituent at its C-6 position.

Keywords: 3-phosphonocoumarin; 1,2-benzoxaphosphorin; coumarin-3-carboxylates; Pd-catalyzed reactions; cross-coupling; Suzuki reaction; Sonogashira reaction; photophysical properties; fluorescence; DFT calculations



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1. Introduction

The presence of the coumarin structure in natural products and biologically active molecules has promoted considerable interest toward their synthesis [1–3]. The coumarin framework is widely used as a building block for obtaining derivatives that exhibit a wide variety of biological properties [4], especially anti-HIV, antitumor, anticoagulant, and antibiotic activities [5]. Moreover, some representatives of this class of compounds were screened as new drug candidates showing promising inhibition activity against the main protease of SARS-CoV-2 (PDB ID: 5N5O) [6,7].

Furthermore, the photophysical properties of coumarin-based fluorescent dyes have shown the advantage of using the benzopyran moiety as a fluorogenic scaffold [8]. Various coumarin-based compounds were applied in fields as laser dyes [9], cell-imaging biomarkers [10], and optical brighteners [11].

The synthesis of substituted coumarins is still dominated by classical methods, such as the Knoevenagel, Perkin, and Pechmann reactions [12–14], which although powerful and proven, have limited scope in terms of functional group compatibility. Recent studies have centered on the use of palladium-catalyzed cross-coupling C–C bond formation leading to the 3-, 4- and 6-substituted coumarins [15–19]; thus the number of Pd-catalyzed approaches for obtaining coumarins is constantly growing [20–22]. However, most of these synthetic protocols are focused on monosubstituted coumarins. Only limited applications of metal-catalyzed reactions for the synthesis of benzene ring-functionalized 3-substituted coumarins, especially when electron withdrawing groups are present, have

been reported [23–25]. Therefore, herein we present an efficient method for the synthesis of fluorescent coumarins and phosphorous-containing coumarin-type heterocycles via palladium cross-coupling reactions, whereby the visible absorption properties of the compounds can be controlled by introducing various C-3 and C-6 substituents directly to the heteroaromatic structure.

2. Results and Discussion

2.1. Theoretical Investigation of Substituted 3-Phosphonocoumarin Structures—Evaluation of the Fluorescent Properties

As a part of our systematic investigation on the chemical behavior of 3-phosphonocoumarin, 1,2-benzoxaphosphorin, as well as other 3-substituted coumarins, we theoretically studied the possibility to obtain substituted fluorescent species, where a “push–pull” effect with the substituent in the 3-rd position could be observed.

To check the photophysical properties and the possibility of fine tuning the spectral properties of phosphorous-containing model coumarins, quantum-chemical calculations of a series of phosphonocoumarins in acetonitrile as a solvent media were performed. For this purpose, density functional theory (DFT) [26–29] and time-dependent (TD) DFT [30,31] with the Gaussian16 suite of programs [32] were used.

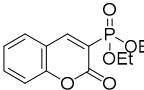
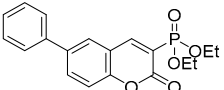
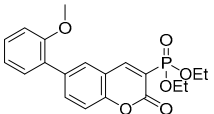
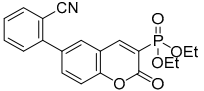
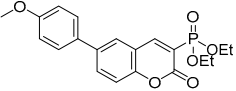
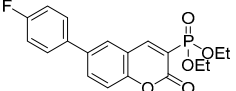
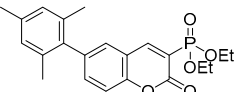
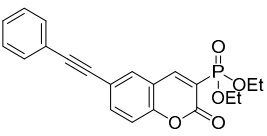
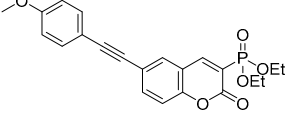
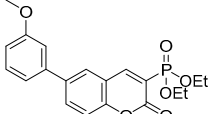
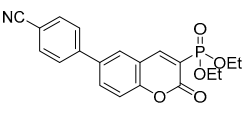
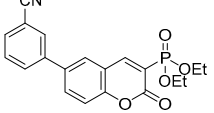
The absorption and emission spectra of several compounds (**CM-1**—**CM-12**, Table 1), varying the substituent in position C-6 of the coumarin ring were calculated. Based on previous investigations in our group, coumarins bearing substituents in position C-6 [33] and C-7 [34] exhibit good fluorescent properties. The model compounds phenyl and aryl groups were chosen to enlarge the conjugated system, connected to the coumarin fragment. In order to take the solvent effect into account, an implicit solvent model (PCM) was used. The long-range corrected hybrid exchange–correlation functional CAM-B3LYP [35] paired with 6-31++G** basis set was employed [36].

The calculated absorption and emission energies of the phosphorous-containing coumarins were compared—structure **CM-1** and models having either EDG (electron-donating group) or EWG (electron withdrawing group) in 6-th position of the coumarin ring (**CM-2** to **CM-12**). The calculations showed that the chosen structures bearing different substituents red-shifted the absorption by 4–32 nm compared to the unsubstituted one (**CM-1**). This shift to a longer wavelength indicates that the differently substituted aryl groups have a significant impact on the absorbance of the coumarin derivatives.

The absorption spectra of structure **CM-5** with a p-methoxyphenyl group in position C-6 is more red-shifted compared to its *ortho*-isomer (**CM-3**), 320 nm versus 312 nm, respectively. For the model-bearing methoxy group in *meta* position, **CM-10**, the value for λ_{abs} is 309 nm. The absorption and the emission wavelengths of the model **C-10** are very similar to the non-substituted phenyl-bearing coumarin model **CM-2**. As expected, due to the lack of conjugation between the substituent and the coumarin moiety, an MeO-group in *meta* position would not affect the photochemical properties of the phosphorous-containing coumarin. This shows that not only the nature of the substituent in the phenyl ring is important, but also its position. It could be assumed that better conjugation occurs when there is an electron-donating group in *para*-position in the aryl substituent; therefore, the push–pull effect tends to be stronger.

In order to check whether a phenyl group (structure **CM-2**) could influence the spectral properties of the compound compared to the unsubstituted 3-phosphonocoumarin (**CM-1**), calculations of the absorption spectra data were performed. The λ_{abs} value for **CM-2** compound is 14 nm red-shifted compared to the one for **CM-1**; the same trend was observed for the emission of these molecules, Table 1. Therefore, a scrupulous selectivity of the substituents could efficiently be used to tune the fluorescent properties of the coumarins.

Table 1. Calculated excitation— λ_{abs} and emission wavelengths— λ_{em} , f —oscillator strengths, Stokes shifts.

Calculated Models (CM)	Structure	λ_{abs} (nm)	f_{abs}	λ_{em} (nm)	f_{em}	Stokes Shift, (nm)
CM-1		295	0.2800	344	0.4989	49
CM-2		309	0.3305	378	0.2419	69
CM-3		312	0.2574	386	0.1802	74
CM-4		299	0.4665	357	0.3821	58
CM-5		320	0.2703	404	0.2480	84
CM-6		310	0.3446	378	0.2513	68
CM-7		299	0.5267	372	0.2611	73
CM-8		319	0.3404	384	0.3114	65
CM-9		327	0.2703	402	0.2480	75
CM-10		309	0.3569	374	0.2826	66
CM-11		304	0.4667	363	0.3832	59
CM-12		304	0.4195	364	0.3230	61

The effect of EWG in the aryl substituent was also considered. Two models having -CN or -F group were tested. The spectral properties of structure **CM-4**, containing CN-group in *ortho*-position, were investigated and the presence of this group lowers the λ_{abs} value, Table 1. When the CN-group is at *para* or *meta* position, **CM-11** and **CM-12**, the absorption maximum for both structures is slightly bathochromically shifted by 5 nm compared to the value for **CM-4** model, which is 299 nm. Comparing the calculated absorption of **CM-1**

with **CM-6**, the 15 nm red-shift indicates that a minor change in the UV-spectra could be made when a fluorine atom is introduced in the aryl substituted.

Moreover, the effect of the alkyl groups in the aryl substituent (mesityl group), **CM-7**, was evaluated. The absorption wavelength of the compound is slightly red-shifted (only 4 nm) compared to **CM-1**. The presence of mesityl group (**CM-7**) would suppress the fluorescent properties compared to the phenyl substituent (**CM-2**), but still the emission is slightly red-shifted, compared to **CM-1**.

The possibility of having a longer conjugated system was also considered. Two compounds having triple C≡C bond were investigated (**CM-8** and **CM-9**). Comparing their emission to the one of **CM-1** (384 nm for **CM-8**, 402 nm for **CM-9**, and 344 nm for **CM-1**) indicates that the presence of an elongated π -system is beneficial to the fluorescent properties of the coumarin derivatives. In addition, (in **CM-9**) the presence of a methoxy group at *para*-position leads to higher λ_{em} compared to **CM-8**. Interestingly the emission for the model compounds **CM-2** and **CM-8** (having phenyl groups, 378 nm and 384 nm, respectively) and **CM-5** and **CM-9** (404 nm and 402 nm, respectively) slightly differ; therefore the addition of a triple bond does not affect the fluorescence properties of the coumarin species. The models bearing CN-group (**CM-4**, **CM-11**, and **CM-12**) exhibit emission maxima at a shorter wavelength (around 360 nm) compared to the structure having unsubstituted phenyl ring **CM-2**.

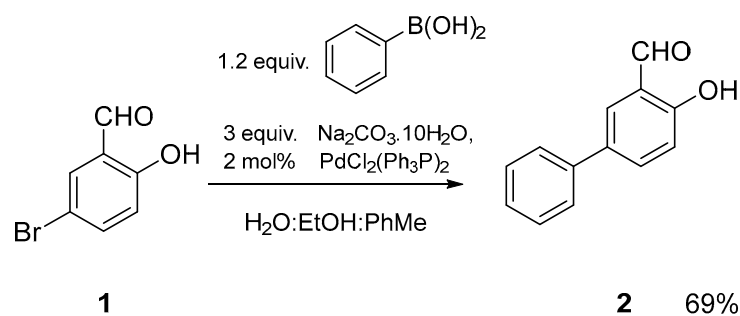
The calculated Stokes shifts for all the compounds were compared to the unsubstituted phosphorous coumarin **CM-1** (49 nm), Table 1. The absolute values of the calculated shifts for all the substituted compounds (**CM-2–CM-9**) are higher (64–84 nm) than the Stokes shift for **CM-1**. Compound **CM-4** bearing -CN group in the aryl moiety has the lowest calculated Stokes shift (58 nm) in comparison to all of the substituted coumarin derivatives. The highest one was calculated for structure **CM-5** that might be due to the EDG group in *para*-position in the aryl group.

The obtained theoretical results imply that the optical properties of phosphorous-containing coumarin systems can be tuned by altering the substituent in its C-6 position. These findings motivate us to synthesize the model structures that possess promising fluorescent properties and to experimentally check the spectral properties of the substituted 3-phosphonocoumarins.

2.2. Synthesis of Fluorescent Coumarins and Phosphorous Containing Coumarin-Type Heterocycles

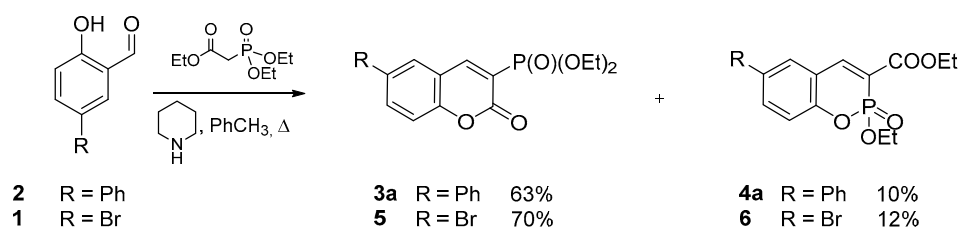
To obtain the calculated substituted fluorescent species, where a “push-pull” effect with the substituent in 3-rd position could be observed, a Pd-catalyzed cross-coupling reaction and in particulate the Suzuki–Miyaura coupling, was investigated.

The Knoevenagel reaction, as one of the classical cyclization methods, was the first tested approach to obtain the desired structures. For this purpose, the phenyl substituted salicylaldehyde **2** had to be synthesized. One of the possible reaction paths includes adding the desired phenyl fragment via the Suzuki coupling starting from 5-bromo-2-hydroxybenzaldehyde **1**, Scheme 1. The reaction of compound **1** with phenylboronic acid was performed by using sodium carbonate decahydrate as a base in mixed solvent media (toluene:ethanol:water) and was catalyzed via bis(triphenylphosphine)palladium(II) dichloride (2 mol%) in inert atmosphere for 24 h at 80 °C. The yield of the arylated product **2** was moderate—69%. This compound was previously synthesized with slightly better yield using different base and solvent media, however, applying 10 mol% of the palladium catalyst [37].



Scheme 1. Suzuki reaction of 5-bromo-2-hydroxybenzaldehyde **1** with phenylboronic acid.

The isolated 2-hydroxy-5-phenylbenzaldehyde **2** was used as a starting material in the Knoevenagel reaction with triethyl phosphonoacetate. It should be mentioned that compound **2** is not very stable—it slowly oxidized in air, both at room temperature or when stored at 4–10 °C. The condensation reaction was carried out following the procedure developed in our group [38] applying piperidine as a catalyst in dry toluene at reflux, Scheme 2.



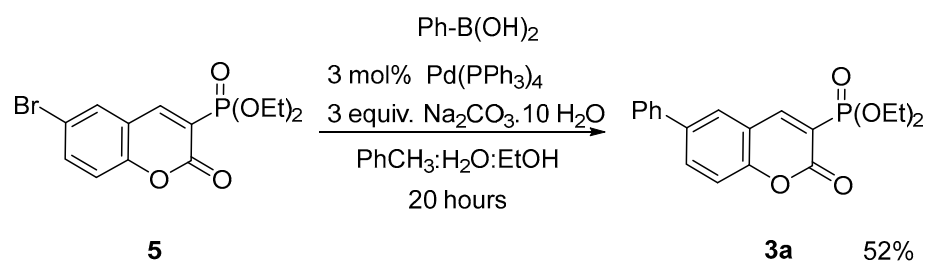
Scheme 2. Knoevenagel condensation.

The reaction was completed in 5 h. Even though the reaction went smoothly, there were some difficulties related to the evaporation of the solvent and the separation of the two chemoisomers. The first obstacle was that compounds **3a** and **4a** have similar R_f -values on both silica and alumina (TLC-monitoring); therefore, it was difficult to separate the compounds to sufficient purity by column chromatography. On the other hand, both compounds are slowly solidifying oils which made further purification by recrystallization impracticable.

It is interesting to note that the phenyl substituted benzopyrans **3a** and **4a** possess fluorescent properties as calculated. Therefore, a parallel approach for obtaining these structures was planned based on the preparation of 6-bromo-3-phosphonocoumarin **5** by Knoevenagel condensation of 5-bromo-2-hydroxybenzaldehyde **1** with triethyl phosphonoacetate [38], Scheme 2, followed by a subsequent derivatization of the products by Suzuki coupling.

The advantages of this synthetic pathway are the usage of a stable and cheaper aldehyde and mainly the easier separation and further purification by column chromatography of products **5** and **6**.

Thereafter, the reaction of 6-bromo-3-phosphonocoumarin **5** with phenylboronic acid, Scheme 3, was carried out using a relatively high load of palladium catalyst (3 mol%) due to the electron-donating oxygen atom from the lactone, bonded to the benzene ring in the coumarin moiety.



Scheme 3. Suzuki coupling.

During the preliminary studies, some unexpected problems were faced due to the similar chromatographical behavior of compound **5** and the desired product **3a**. This complicated the TLC monitoring of the reaction and the purification of diethyl 6-phenylcoumarin-3-phosphonate **3a**. Formation of the dehalogenated coumarin structure **7** was also observed as a side product. Therefore, better reaction conditions needed to be developed for full conversion of **3b** where no side reaction could be observed.

The optimal conditions for the palladium-catalyzed coupling were determined through a series of experiments in which different combinations of catalyst (Figure 1) and solvent were applied. Two groups of palladium catalysts were employed, differing by the Pd oxidation state—Pd(0) and Pd(II), and by the coordinated ligand—phosphine and NHC-type.

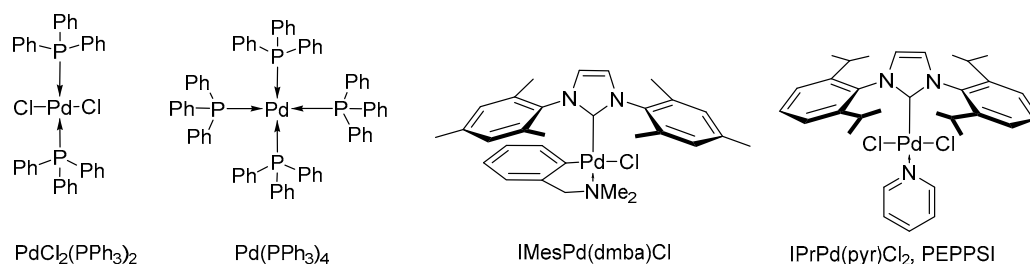
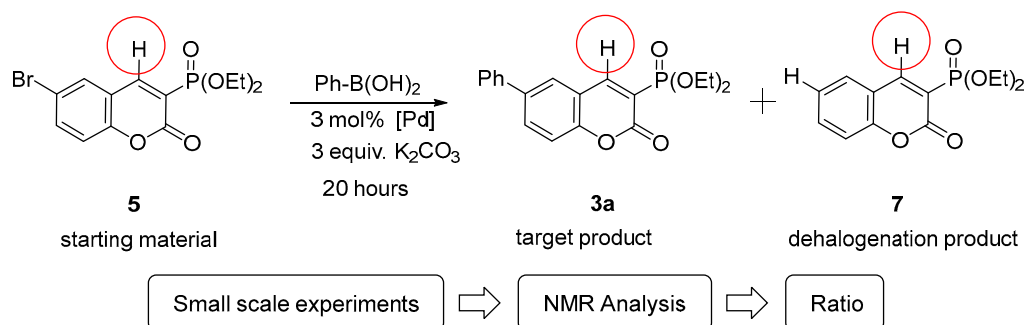


Figure 1. Pd-complexes used as catalyst in the studied reaction.

Due to the drawbacks mentioned above, a series of small-scale experiments were performed, Scheme 4, Table 2. The ratio of compounds **5**, **3a**, and **7** was monitored by NMR spectroscopy of the crude reaction mixture. Based on the chemical shift of the H-4 proton in all coumarin species **5**, **3a**, and **7**, the ratio of the compounds was determined.



Scheme 4. Suzuki coupling—optimizing the conditions.

Table 2. Ratio of the formed products in the crude reaction mixture *.

Entry	Solvent	5	3a	7	Catalyst
1	PhCH ₃	traces	>99	traces	PdCl ₂ (PPh ₃) ₂
2	PhCH ₃ :H ₂ O	traces	>99	traces	PdCl ₂ (PPh ₃) ₂
3	Dioxane	~14	~86	traces	PdCl ₂ (PPh ₃) ₂
4	Dioxane:H ₂ O	traces	>99	traces	PdCl ₂ (PPh ₃) ₂
5	EtOH:H ₂ O:PhCH ₃	traces	>99	traces	PdCl ₂ (PPh ₃) ₂
6	PhCH ₃	~54	~45	traces	Pd(PPh ₃) ₄
7	PhCH ₃ :H ₂ O	18	74	7	Pd(PPh ₃) ₄
8	Dioxane	~54	~45	traces	Pd(PPh ₃) ₄
9	Dioxane:H ₂ O	25	68	6	Pd(PPh ₃) ₄
10	EtOH:H ₂ O:PhCH ₃	~34	~65	traces	Pd(PPh ₃) ₄
11	PhCH ₃	~57	~42	traces	IMesPd(dmba)Cl
12	PhCH ₃ :H ₂ O	traces	>99	-	IMesPd(dmba)Cl
13	Dioxane	~56	~43	traces	IMesPd(dmba)Cl
14	Dioxane:H ₂ O	traces	>99	traces	IMesPd(dmba)Cl
15	EtOH:H ₂ O:PhCH ₃	traces	>99	traces	IMesPd(dmba)Cl
16	PhCH ₃	30	70	-	PEPPSI-type
17	PhCH ₃ :H ₂ O	-	100	-	PEPPSI-type
18	Dioxane	24	76	-	PEPPSI-type
19	Dioxane:H ₂ O	-	100	-	PEPPSI-type
20	EtOH	?	?	?	PEPPSI-type
21	EtOH:H ₂ O	traces	~77	~23	PEPPSI-type
22	EtOH:H ₂ O:PhCH ₃	traces	94	5	PEPPSI-type

* The ratio is determined by NMR-spectroscopy.

For better comparison of the obtained results, the same reaction time was implied for all of the listed small-scale reactions (20 h). The reactions were performed using 1.2 equiv. of phenylboronic acid under an argon atmosphere at 80 °C. According to the literature data [39–41], addition of water as a co-solvent or other protic solvent to the mixture might improve the outcome of the reaction; thus, several combinations of water or ethanol with dry toluene or dioxane were also tested. Potassium carbonate (3 equiv.) was tested as a base for the reaction with the coumarin species due to the possibility of opening the lactone ring if stronger bases were used [42,43]. Not only did the replacement of the sodium carbonate with potassium carbonate improve the yields significantly but also K₂CO₃ is nontoxic, cheap, and strong enough to activate [44–48] all of the used Pd(II) catalysts. The results of the initial experiments are summarized in Table 2.

The catalysts were introduced as a solution in THF (0.5 mL) except for PdCl₂(PPh₃)₂. Due to its insolubility, this catalyst was introduced to the reaction in its crystalline form. To properly evaluate the obtained results for PdCl₂(PPh₃)₂, 0.5 mL THF was additionally added to the reaction.

As we mentioned above, the reaction was performed in the presence of different types of palladium catalyst according to the ligands coordinated to the metal atom. The catalytic activity of the phosphine type complexes PdCl₂(PPh₃)₂ and Pd(PPh₃)₄ in the studied reaction differed significantly. The usage of the PdCl₂(PPh₃)₂ in the arylation reaction led to almost full conversion of the starting 6-bromo-3-phosphonocoumarin 5. As it could be seen from the listed results, Table 2, when employing bis(triphenylphosphine)palladium(II) dichloride, the reaction outcome is almost solvent-media-independent. However, not only the starting material but also the dehalogenated coumarin 7 was observed in the crude reaction mixture. The catalytic activity of tetrakis(triphenylphosphine)palladium(0) with the presented coumarin 5 was not satisfying—Pd(PPh₃)₄ complex gave the worst results amongst all of the chosen catalytic systems. However, when a mixed solvent (toluene:water or dioxane:water; entry 7 and entry 9, Table 2) was used, the yield of the desired product was increased.

The next set of experiments was performed by palladium complexes coordinating NHC-ligands. Two catalysts having bulkier ligands were tested in the Suzuki coupling—IMesPd(dmba)Cl and PEPPSI-type. The main observation in the IMesPd(dmba)Cl catalyzed reactions was the conversion and the yield of the targeted product. The selectivity of the reaction increased when water was introduced in the solvent media, [entry 12](#) and [entry 14](#), [Table 2](#).

The full conversion of the 6-bromo-3-phosphocoumarin **5** into 6-phenyl-3-phosphonocoumarin **3a** was observed only when the reaction was carried out under the conditions listed as [entry 17](#) and [entry 19](#) ([Table 2](#)) in the presence of the PEPPSI-type catalyst.

It is interesting to note that when the reaction was performed in ethanol as a solvent media, a full conversion of the starting product was observed; however, the formation of **3a** was not detected. This statement was based on the NMR spectra where the characteristic signals for the protons at position C-4 for neither the **5**, **3a**, or **7** were found. This might be due to opening of the lactone ring in the presence of ethanol/base as it was previously reported [[42,43,49–52](#)].

Further scrutiny of the solvent media gave additional clarity of the overall conditions for better coupling reactivity. This made us consider the combination of PEPPSI-type catalyst and dioxane/water or toluene/water as the most effective in accomplishing high cross-coupling yield with full conversion of the starting material. The combination of toluene/water was preferred for the next Pd-catalyzed coupling reactions because of its low toxicity and price.

The structure of the 6-phenyl-3-phosphonocoumarin **3a** was determined by a single crystal X-ray analysis (CCDC 2209998, [Figure 2](#)) where only one substance was identified in the crystalline matter.

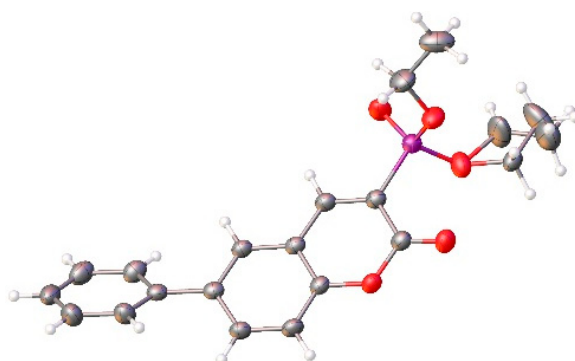
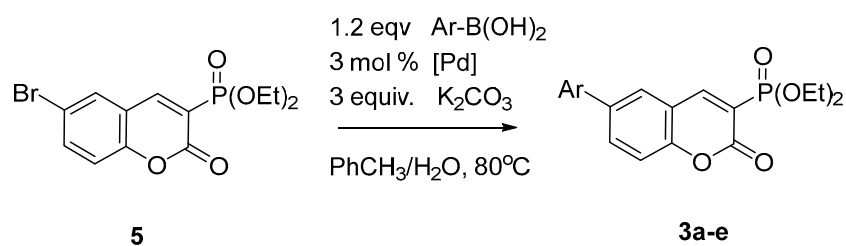


Figure 2. ORTEP representation with thermal ellipsoids 40%—**Crystal Data** for $C_{19}H_{19}O_5P$ ($M = 358.333$ g/mol): monoclinic, space group $P2_1/n$ (no. 14), $a = 13.6869(9)$ Å, $b = 8.5123(5)$ Å, $c = 14.9033(9)$ Å, $\alpha = 90^\circ$, $\beta = 90.726(2)^\circ$, $\gamma = 90^\circ$, $V = 1736.20(19)$ Å³, $Z = 4$, $T = 133.00$ K, $\mu(M_{oK\alpha}) = 0.185$ mm⁻¹, $D_{calc} = 1.371$ g/cm³, 26,401 reflections measured ($4.06^\circ \leq 2\theta \leq 55.84^\circ$), 4155 unique ($R_{int} = 0.0591$, $R_{sigma} = 0.0405$) which were used in all calculations. The final R_1 was 0.0390 ($I > 2\sigma(I)$) and wR_2 was 0.1092 (all data). The crystallographic data could be found in the Supplementary Materials.

The cross-coupling reactivity of 6-bromo-3-phosphonocoumarin **5** was further tested under the above-optimized conditions, [Scheme 5](#). Aiming to increase the conjugation of the push–pull system, a series of boronic acids bearing electron donating and electron withdrawing groups were chosen, [Table 3](#). The reactions were performed in five-time larger scales compared with the preliminary studies illustrated in [Table 2](#).



Scheme 5. Suzuki coupling of 6-bromo-3-phosphonocoumarin **5**.

Table 3. Parameters, reagents, and products of palladium-catalyzed arylation of 6-bromo-3-phosphonocoumarin **5**.

Entry	Boronic Acid	Product	[Pd]	Time, [h]	Yield *, [%]
1			PEPPSI-type	17 h	90%
2			PEPPSI-type	120 h	41%
3			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	48 h	63%
4			PEPPSI-type	48 h	95%
5			PEPPSI-type	48 h	61%
6			PEPPSI-type	48 h	19%
7			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	48 h	45%

* Isolated yields after column chromatography.

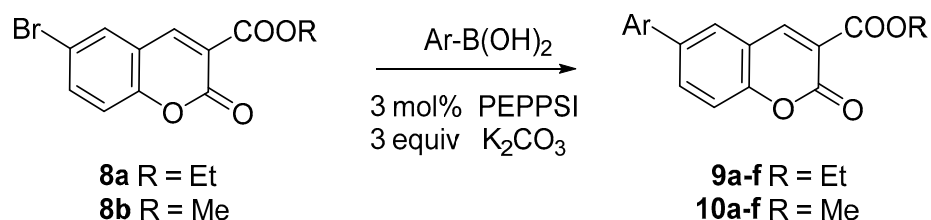
Interestingly, under the optimized reaction conditions and in the presence of the selected boronic acid, the cross-coupling reaction with 6-bromo-3-phosphonocoumarin **5** could be achieved, Table 3, Scheme 5. In cases of unsubstituted or *para*-substituted boronic acids, the yields of the desired products **3a**, **3c**, and **3d** varied from good to almost quantitative (61–95%) after purification by column chromatography. In all the presented experiments, the time needed for the full conversion of the coumarin **5** when substituted boronic reagents were used had increased compared with the unsubstituted phenylboronic acid. This implies that the hindrance of the reaction center and the electronic effect of the groups play a major role in the outcome of the reactions.

As a proof of that hypothesis, we observed that when the reaction center of the boronic reagent is hindered, the yield of the products **3b** and **3e** were low (entry 2 and entry 6, Table 3) using PEPPSI-type catalyst. The more hindered the boronic adduct is, the less yield is obtained. This observation is not new when a Suzuki reaction is performed with *ortho* or *di-ortho* substituted boronic species [53,54]; therefore, we decided to test other not so voluminous palladium catalysts that have shown good catalytic activity in the initial reaction with **5**. The arylation was performed with $\text{PdCl}_2(\text{PPh}_3)_2$ (entry 3 and entry 7) thus

resulting in significantly increasing of the yields for product **3b** and **3e**, from 41% to 63% and from 19% to 45%, respectfully.

Even when using less hindered catalyst, [entry 7, Table 3](#), the reaction with mesityl boronic acid gave the lowest yields in comparison with the other arylated products. Thence, an experiment for obtaining **3e** with better yields was performed where the reaction temperature was increased to 100 °C; however, this did not give the positive outcome that we expected. The catalyst slowly decomposed, and only partial conversion of the starting material was indicated.

Phosphorus-containing coumarins such as **7** [[1](#)] are of a great importance in the areas of *LiveScience* due to the similarity of phosphorous compounds to the naturally occurring carboxylic acid derivatives and their potential application in varies biological systems. In order to further explore the generality of our modified procedure and to obtain analogous structures, the chemical behavior of halogenated ethyl and methyl ester of coumarin-3-carboxylic acid **8a,b** was studied in the Suzuki reaction, [Scheme 6](#).



Scheme 6. Palladium-catalyzed arylation of 6-bromocoumarin-3-carboxylates **8a,b**.

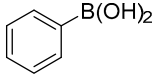
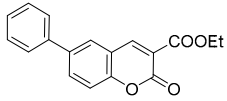
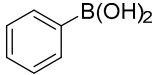
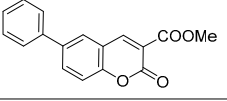
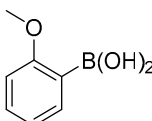
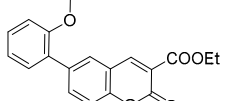
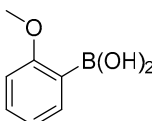
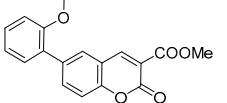
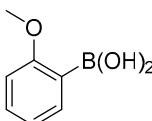
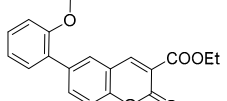
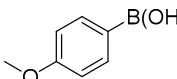
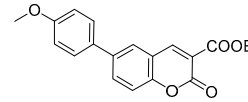
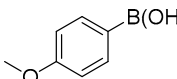
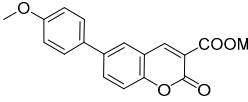
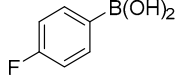
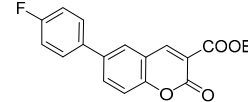
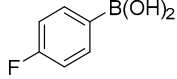
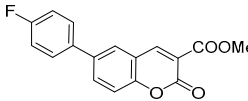
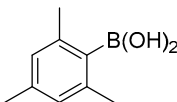
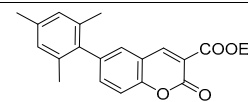
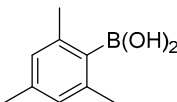
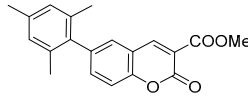
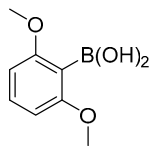
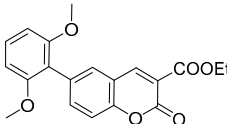
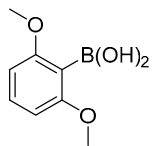
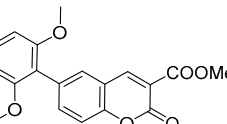
The same reaction conditions—PEPPSI-type catalyst, mixed solvent (toluene:water) and potassium carbonate as a base—were employed in for the reactions with ethyl and methyl ester of coumarin-3-carboxylic acid **8a,b**. A striking observation was the extreme reactivity of the bromo carboxylates in the Suzuki reaction catalyzed by the PEPPSI complex. For example, the time needed for full conversion of both starting materials, in case of unsubstituted or substituted in *para*-position boronic acid, was determined to be in the range of 30 to 60 min.

Longer reaction time and lower yields were observed again when 2-methoxyphenyl boronic acid was used as an adduct in the Suzuki reaction with coumarin **8a**, [entry 3, Table 4](#). The replacement of the bulky PEPPSI-type catalyst with less hindered complex as $\text{PdCl}_2(\text{PPh}_3)_2$ resulted in increasing the yield from 20% to 68% ([entry 4, Table 4](#)). The usage of bis(triphenylphosphine)palladium(II) dichloride gave us the opportunity to obtain coumarin derivatives with even more hindered boronic acids—as 2,4,6-trimethylphenyl boronic acid and 2,6-dimethoxyphenyl boronic acid ([entry 10–13, Table 4](#)).

A weak reactivity of the coumarin species in the studied conditions in cases listed as [entry 10–13](#) was observed. The obtained low yields for products **9e,f** and **10e,f** might be due not only to the fact that there was not full conversion of the esters but also to difficulties in their purification.

Longer reaction time and lower yields were observed again when 2-methoxyphenyl boronic acid was used as an adduct in the Suzuki reaction with coumarin **8a**, [entry 3, Table 4](#). The replacement of the bulky PEPPSI-type catalyst with less hindered complex as $\text{PdCl}_2(\text{PPh}_3)_2$ resulted in increasing the yield from 20% to 68% ([entry 4, Table 4](#)). The usage of bis(triphenylphosphine)palladium(II) dichloride gave us the opportunity to obtain coumarin derivatives with even more hindered boronic acids—as 2,4,6-trimethylphenyl boronic acid and 2,6-dimethoxyphenyl boronic acid ([entry 10–13, Table 4](#)).

Table 4. Parameters, reagents, and products of palladium-catalyzed arylation of 6-bromocoumarin-3-carboxylates **8a,b**.

Entry	Boronic Acid	Product	[Pd]	Time	Yield *, [%]
1		 9a	PEPPSI-type	30 min	90%
2		 10a	PEPPSI-type	60 min	97%
3		 9b	Pd(PPh ₃) ₂ Cl ₂	24 h	68%
4		 10b	Pd(PPh ₃) ₂ Cl ₂	21 h	83%
5		 9b	PEPPSI-type	48 h	20%
6		 9c	PEPPSI-type	45 min	92%
7		 10c	PEPPSI-type	45 min	99%
8		 9d	PEPPSI-type	45 min	80%
9		 10d	PEPPSI-type	60 min	99%
10		 9e	Pd(PPh ₃) ₂ Cl ₂	72 h	29%
11		 10e	Pd(PPh ₃) ₂ Cl ₂	90 h	18%
12		 9f	Pd(PPh ₃) ₂ Cl ₂	72 h	complex mixture
13		 10f	Pd(PPh ₃) ₂ Cl ₂	72 h	complex mixture

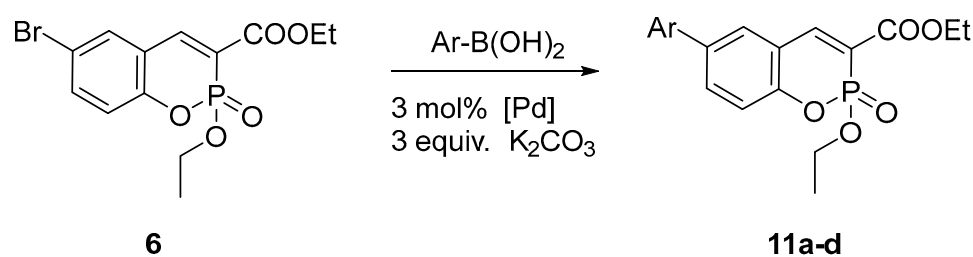
* Isolated yields after column chromatography.

The synthesis of compounds **9a,c,d** via the Suzuki reaction was previously reported by two different research collectives [23,24]; however, different catalytic systems were used. The obtained yields for these compounds were lower under longer reaction times. For example, Gobec et al. [24] obtained the ethyl 6-phenylcoumarin-3-carboxylate **9a** with only 33% yield, while the reaction time was not specified (overnight); Carbonaro et al. [23]

reported the formation of product **9a** in 55% yield for 12–16 h. In the procedure that we developed, the ethyl 6-phenylcoumarin-3-carboxylate **9a** was isolated with 90% yield after only 30 min, entry 1 (Table 4). The yield of compound **9c** was reported to be 67% (overnight) [24] and 66% (12–16 h) [23]. Using the optimized procedure based on the PEPPSI-type catalyst, we managed to isolate the ethyl 6-(4-methoxyphenyl)coumarin-3-carboxylate **9c** in 92% for 45 min, entry 6 (Table 4). The yield of **9d** obtained from a Suzuki reaction catalyzed by Pd(PPh₃)₄ was reported [24] to be 54% (overnight). As can be seen from Table 4, changing the catalytic system could significantly increase the reactivity of the coumarin **8a**, thus resulting in the 80% yield for coumarin **9d** and the conversion time of 45 min, entry 8.

The reactivity of 6-bromocoumarin-3-carboxylates **8a,b** was tested with even bulkier adduct—2,6-dimethoxyboronic acid, entry 12 and entry 13, Table 4. Unfortunately, in both cases, no full conversion of the starting compounds was observed. Even though the reaction times were long, a complexed mixture was obtained, and none of the structures were isolated due to the absence of predominant product. Another drawback was the similar chromatographic properties of some components of the mixture on both silica and alumina.

Motivated by these results, we next sought to expand the scope of the optimized procedure to the arylation of a more challenging substrate, such as 1,2-benzoxaphosphorin **6**, Scheme 7.



Scheme 7. Palladium-catalyzed arylation of ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **6**.

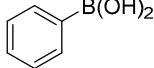
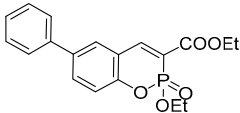
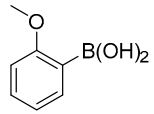
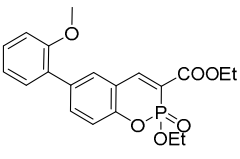
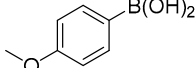
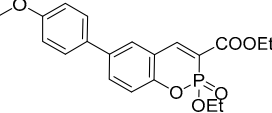
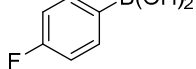
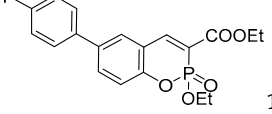
Under the optimized reaction conditions—PEPPSI-type catalyst, solvent mixture of toluene:water, potassium carbonate and in the presence of the selected boronic acid—the cross-coupling reaction with ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **6** was achieved, Scheme 7, Table 5. The yields for the arylated products **11a–d** are similar to the ones obtained for the corresponding chemoisomeric structures **3a–d**. However, the time needed for the consumption of the starting material compared with the 3-phosphonocoumarin derivatives was shorter.

A different catalyst was used, Pd(PPh₃)₂Cl₂ (entry 3, Table 5), only when 2-methoxyphenylboronic acid was employed. The bis(triphenylphosphine)palladium(II) dichloride complex gave better results with the studied carboxylates and with 6-bromo-3-phosphonocoumarin **5**. However, in the case of oxaphosphorine-3-carboxylate **6**, the yield of product **11b** was moderate (45%).

In the studied reaction conditions, poor reactivity of the coumarin species was observed with respect to hindered boronic acids; therefore, no experiments were performed with 2,4,6-trimethylphenylboronic acid and 2,6-dimethoxyphenylboronic acid. On the other hand, oxaphosphorine-3-carboxylate **6** is a byproduct, and there is still no efficient method for its preparation on a large scale.

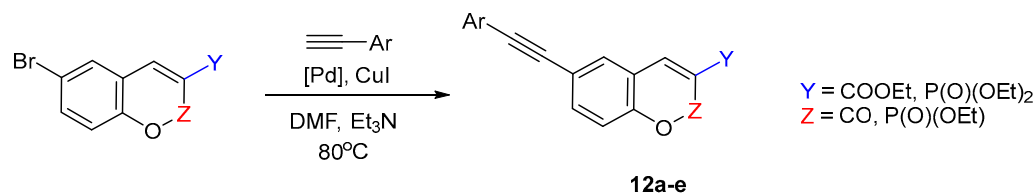
The Suzuki reaction of ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **6** is applicable for boronic acids bearing electron-donating and electron-withdrawing groups. The only limitation of the procedure is when a hindered organoboron substrate is used.

Table 5. Parameters, reagents, and products of palladium-catalyzed arylation of ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **6**.

Entry	Boronic Acid	Product	[Pd]	Time, [h]	Yield *, [%]
1		 11a	PEPPSI-type	16 h	89%
2		 11b	Pd(PPh ₃) ₂ Cl ₂	42 h	45%
3		 11c	PEPPSI-type	3 h	87%
4		 11d	PEPPSI-type	2.5 h	89%

* Isolated yields after column chromatography.

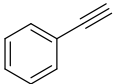
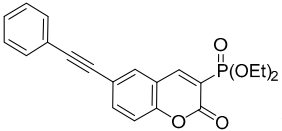
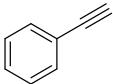
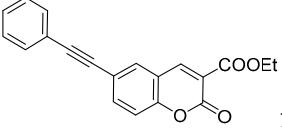
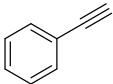
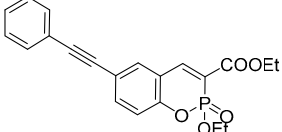
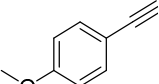
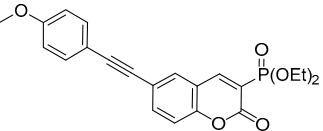
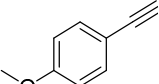
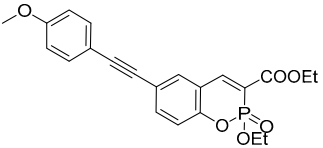
To extend the π -system of the heterocyclic system, another Pd-catalyzed reaction was tested on the studied coumarins—the Sonogashira alkylation, Scheme 8, Table 6.

**Scheme 8.** Palladium-catalyzed alkylation of 3-substituted coumarin species—Sonogashira coupling.

Most reactions with the chosen substrates were performed under classical conditions for Sonogashira coupling [55,56]—Pd(PPh₃)₂Cl₂/CuI as a catalytic system in the presence of Et₃N in DMF at 80 °C under argon atmosphere. To compensate the electron-rich nature of the 4-ethynylanisole, entry 4, Table 6, PEPPSI-type complex was applied. However, these conditions resulted in the formation of product **12d** in only a 56% yield. Reaction of the same alkylation reagent and ethyl coumarin-3-carboxylate **8a** was not carried out since the product is a known compound and was prepared under the same classical conditions [57]. The Sonogashira reaction in analogous conditions involving the methyl carboxylate **8b** had also been reported [58].

Surprisingly, the reactions of ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **6** under the described conditions led to the formation of complexed reaction mixtures, and none of the structures **12c,e** were isolated due to the absence of predominant product.

Table 6. Parameters, reagents, and products of palladium-catalyzed alkylation of 3-substituted coumarin species—Sonogashira reaction.

Entry	Alkyne	Product	[Pd]	Time, [h]	Yield *, [%]
1		 12a	Pd(PPh ₃) ₂ Cl ₂	20 h	82%
2		 12b	Pd(PPh ₃) ₂ Cl ₂	22 h	52%
3		 12c	Pd(PPh ₃) ₂ Cl ₂	48 h	complex mixture
4		 12d	PEPSI-type	30 h	56%
5		 12e	Pd(PPh ₃) ₂ Cl ₂	48 h	complex mixture

* Isolated yields after column chromatography.

2.3. Photophysical Properties

The photophysical properties of the synthesized compounds were experimentally determined by UV-VIS and fluorescent spectroscopy. The absorption and fluorescence spectra of the aryl substituted coumarin, **3a**, were recorded in five different solvents—acetonitrile (MeCN), methanol (MeOH), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), and dichloromethane (DCM), Figure 3, Table 7. The obtained results showed that the solvent slightly affects the position of the longest absorption wavelength band. For example, in the polar protic solvent (MeOH) the absorbance maximum was exhibited at 346 nm, and in the non-polar one—dichloromethane was hypsochromically shifted only by 2 nm (Table 7 and Figure 3). In the emission spectra obtained, MeOH and CH₂Cl₂ bands at 459 nm and at 452 nm, respectively, were observed. Interestingly, although DMSO is an aprotic solvent, the maximum in the fluorescence spectrum was bathochromically shifted only by 1 nm compared to MeOH. The biggest difference was noted in the case of EtOAc—the maximum was blue-shifted by 16 nm with respect to the corresponding in DMSO, which was the most red-shifted one.

The spectral data of the other three coumarins bearing phenyl substituents—**9a**, **10a** and **11a** dissolved in acetonitrile, methanol and dichloromethane demonstrated minor solvatochromic effect from 13 to 16 nm—in MeOH the bands were red-shifted, while in DCM they were blue-shifted, and the maximum in acetonitrile was always between these two maxima (Table 7, Figure 3). Due to the higher solubility of the coumarins in acetonitrile compared to methanol, MeCN was selected as a solvent for all other synthesized derivatives.

The UV-VIS and emission spectra of **3b–e**, **12a**, and **12d** compounds in acetonitrile are shown in Figure 4. As predicted by the DFT calculations, the presence of phenyl substituent in 6-th position of the coumarin ring (**3a**) leads to a redshift both in the absorption and the fluorescence spectra by 19 and 42 nm, respectively, compared to the unsubstituted

substance. The absorption maximum in the UV spectrum of the **3e** bearing mesityl group, was at shorter wavelength like in the simulated one—333 nm in comparison with the corresponding value for **3a**—343 nm. The compounds having methoxy group in *ortho*-position and F-atom in the aryl substituent exhibited maximum at 345 nm, while for Ph-C≡C λ_{\max} was slightly red-shifted by 6 nm. The compound containing methoxyphenyl group in *ortho*-position in the aryl substituent emitted at 493 nm.

The derivative **12a** with triple bond and without OMe group in *para* position exhibits a maximum at a shorter wavelength 461 nm. The largest bathochromic shift in the absorption and emission spectra was observed for the coumarin derivatives with longer conjugated π -system, compounds **3c** and **12d**. They exhibited the same absorption maximum at 356 nm, which by 13 nm red-shifted compared to the corresponding spectra of the phenyl derivate, **3a**, while their emission is shifted to the longest wavelength by 82 and 90 nm for **3c** and **12d**, respectively.

The same trend was observed for the ethyl and methyl coumarin-3-carboxylates and benzoxaphosphorines—the absorption and emission bands' shift was highest when there is *para*-methoxyphenyl substituent (Figure 5) as the fluorescence is very similar to that of the corresponding phosphonocoumarins **3c** and **12d**—546, 543, and 541 nm for **9c**, **10c**, and **11c**, respectively, Figure 6. Thus, the substituent in position C-3 does not affect the fluorescence of the coumarin species. The λ_{\max} in the fluorescence spectra of phenyl derivatives is red-shifted by nearly 50 nm with respect to the unsubstituted coumarins, which for each series are denoted with the number of the parent series followed by H (Table 7).

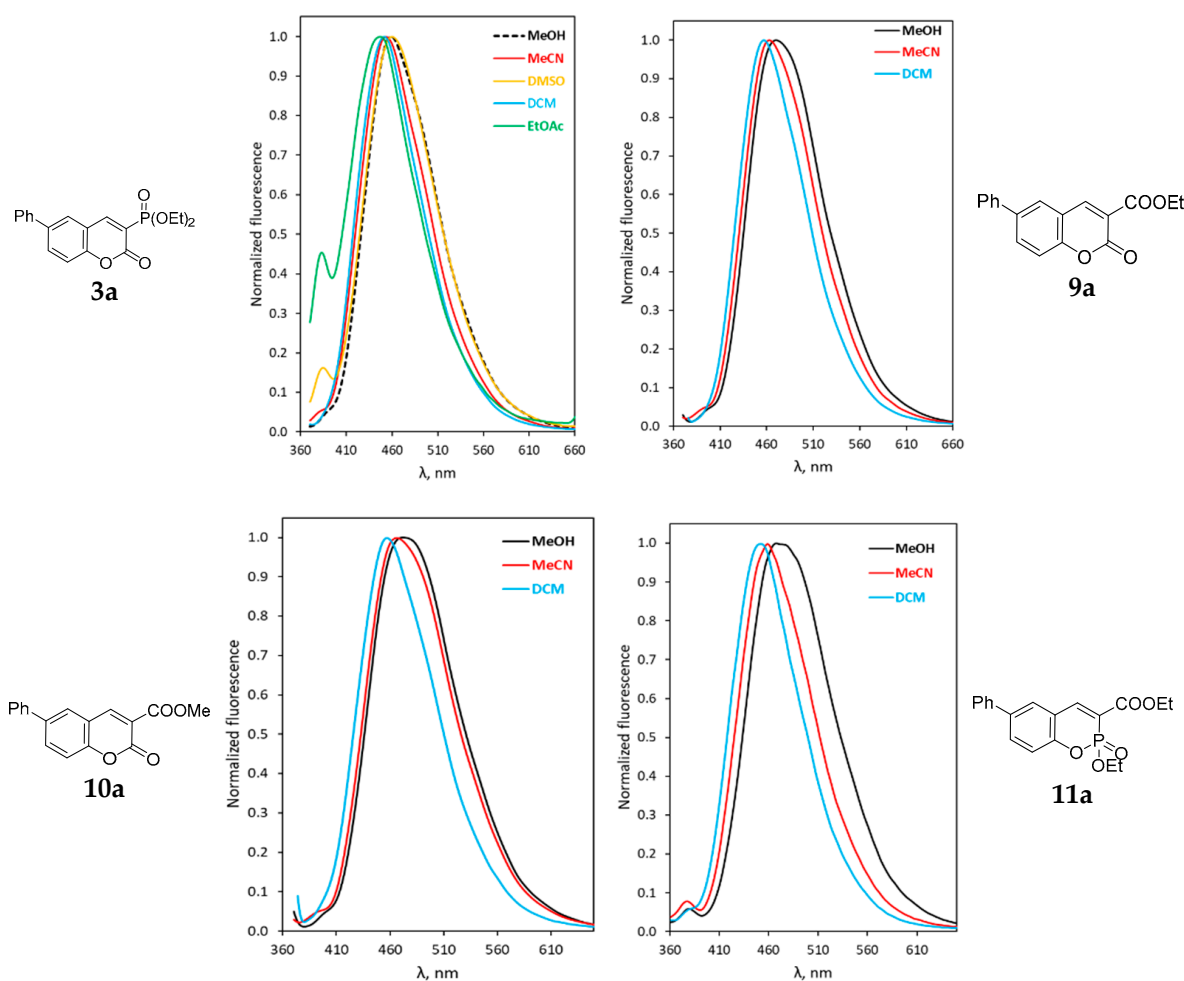
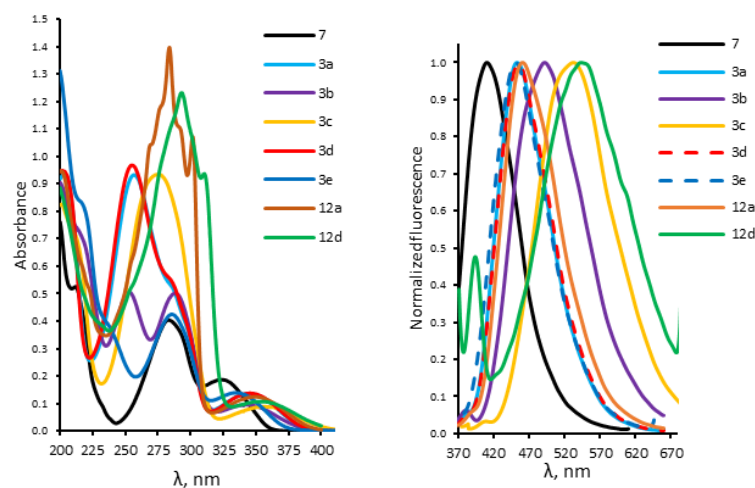


Figure 3. Normalized fluorescent spectra of the phenyl substituted derivatives.

Table 7. Photophysical data of the coumarin derivatives.

Compounds	Solvent	λ_{abs} , nm	λ_{em} , nm	Stokes Shift, nm
7	MeCN	324	411	87
	DMSO	345	460	115
	MeOH	346	459	113
3a	MeCN	343	453	110
	DCM	344	452	108
	EtOAc	343	447	104
3b	MeCN	345	493	148
3c	MeCN	356	535	179
3d	MeCN	345	456	148
3e	MeCN	333	451	118
12a	MeCN	351	461	110
12d	MeCN	356	543	187
9-H *	MeCN	326	412	86
	MeOH	355	470	115
9a	MeCN	355	463	108
	DCM	360	457	97
9b	MeCN	353	503	150
9c	MeCN	366	546	180
9d	MeCN	366	458	92
9e	MeCN	343	458	115
12b	MeCN	357	472	115
10-H *	MeCN	326	411	85
	MeOH	357	472	115
10a	MeCN	353	466	113
	DCM	358	457	99
10b	MeCN	351	504	153
10c	MeCN	363	543	180
10d	MeCN	354	466	112
10e	MeCN	340	460	120
11-H *	MeCN	324	410	86
	MeOH	343	468	125
11a	MeCN	342	459	117
	DCM	342	452	110
11b	MeCN	340	500	160
11c	MeCN	350	541	191
11d	MeCN	341	460	119

* unsubstituted at C-6 in the benzene moiety compounds.

**Figure 4.** UV-VIS and normalized fluorescence spectra of 3a-b, 12a, and 12d phosphonocoumarins in acetonitrile.

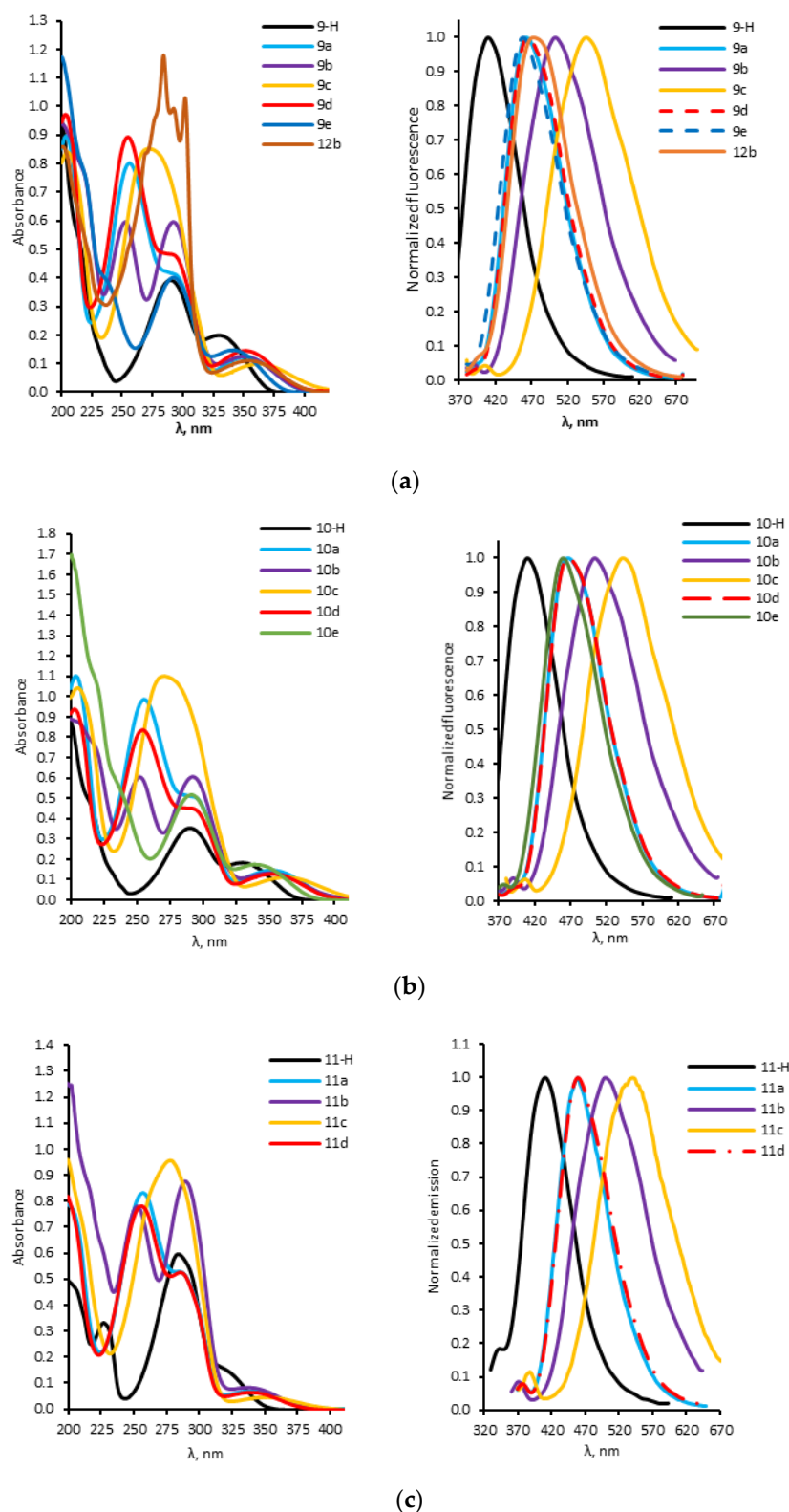


Figure 5. UV-VIS and normalized fluorescence spectra in acetonitrile: (a) series of ethyl coumarin-3-carboxylates compounds **9a–e**, **12b**; (b) series of methyl coumarin-3-carboxylates compounds **10a–e**; (c) series of ethyl 2-ethoxybenzo[e][1,2]oxaphosphorine-3-carboxylate **11a–d**.

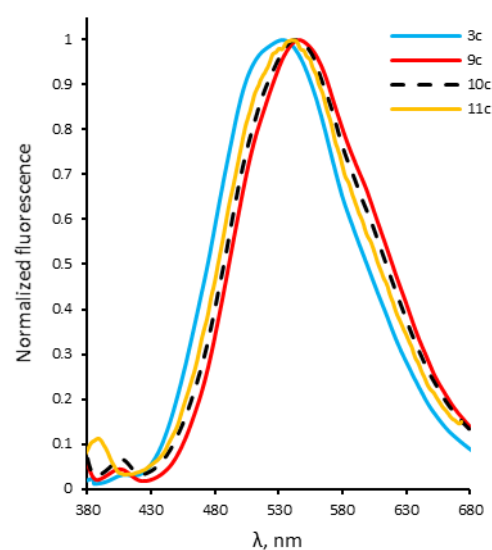


Figure 6. Normalized fluorescence spectra in acetonitrile for derivatives bearing *para*-methoxyphenyl groups.

The observed Stokes shift for all compounds with C-6 substituents was above 100 nm, while the highest was determined for the *para*-methoxyphenyl derivatives, and it varied from 179 for **3c** to 191 for **11c**. For the unsubstituted coumarins, the Stokes shift is smaller and is around 85 nm.

The computed maxima of the absorption spectra, multiplied by the scaling factor, is in very good agreement with the experimental data (Table 8). The differences do not exceed 5 nm. The order of λ_{\max} in the calculated UV spectra is the same as in the experimentally obtained—in direction H-, mesityl-, Ph-, *ortho*-MeOC₆H₄-, F-, Ph-C≡C-, *para*-MeOC₆H₄-, and *para*-MeOC₆H₄-C≡C substituents at position C-6 is the observed bathochromic shift.

Table 8. Comparison between the experimental and calculated spectral characteristics. Scaling factor for the absorbance—1.098 and 1.195—for the emission.

Exp	CM	λ_{abs}^{scaled}	$\Delta\lambda_{abs}^{scaled} - \lambda_{abs}^{exp}$	λ_{em}^{scaled}	$\Delta\lambda_{em}^{scaled} - \lambda_{em}^{exp}$	$\Delta\text{Stokes shift (calc-exp)}$
7	CM-1	324	0	411	0	−38
3a	CM-2	339	−4	452	1	−41
3b	CM-3	343	−2	461	32	−74
3c	CM-5	351	−5	483	52	−95
3d	CM-6	340	−5	452	41	−43
3e	CM-7	328	−5	444	7	−45
12a	CM-8	350	−1	459	2	−45
12d	CM-9	359	3	480	62	−112

The variance for the fluorescence bands in some cases is much more pronounced by up to 62 nm for coumarin **12d**. However, in the results for **3a**, **3e**, and **12a**, the simulated data are red-shifted by only 1, 7, and 2 nm, respectively. The calculated Stokes shift differs by around 40–45 nm. As for the two structures with methoxy group in *para* position, **3c** and **12d**, the distinction is higher and is 95 and 112 nm, respectively.

To test the fluorescent properties of coumarins **3a** and **3c** in different pH, a series of experiments by varying the concentration of sulfuric acid and sodium hydroxide (Figure 7) were performed. Interestingly, the fluorescence of the *para*-methoxyphenyl derivative **3c** was suppressed when lowering the pH of the solution by adding sulfuric acid, while the emission of the phenyl derivative **3a** had increased. This different behavior of the coumarin species might be due to different protonation positions. In compound **3a**, the protonation could occur at the lactone oxygen atom therefore the conjugation would be more effective.

The quenching of the fluorescence of coumarin **3c** might be due to the protonation of the MeO-group which decreases the donor ability of the oxygen atom. The addition of sodium hydroxide might lead to lactone ring opening, thus loss of conjugation (Figure 7c,d).

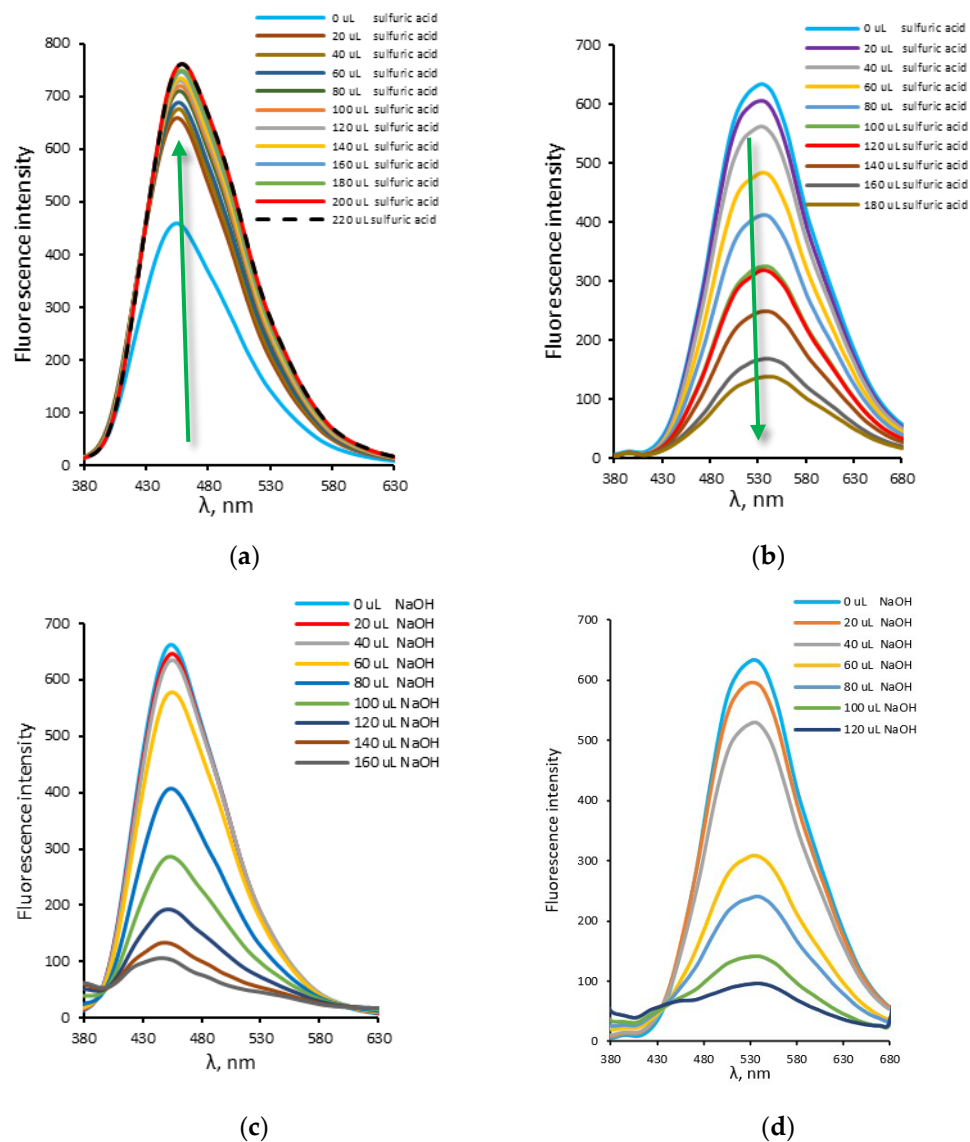


Figure 7. Fluorescence intensity in acetonitrile according to the pH: (a) coumarin **3a** ($c = 10^{-5}$ M) behavior in sulfuric acid, 1N; (b) coumarin **3c** ($c = 10^{-5}$ M) behavior in sulfuric acid, 1N; (c) coumarin **3a** ($c = 10^{-5}$ M) behavior in NaOH, 1N; (d) coumarin **3c** ($c = 10^{-5}$ M) behavior in NaOH, 1N. The green arrow is showing the changing of the fluorescence intensity depending on the H^+ concentration.

3. Materials and Methods

Melting points were determined on an SRS MPA120 EZ-Melt apparatus and are used without correction. The IR spectra were recorded with a Shimadzu FTIR-8400S spectrophotometer. 1H , ^{13}C , and ^{31}P NMR spectra were recorded on a Bruker AVNEO 400 spectrometer (at 400 MHz for 1H , 100.6 MHz for ^{13}C , 376.46 MHz for ^{19}F , and 161.98 MHz for ^{31}P , respectively), Bruker Avance III 500 spectrometer (at 500 MHz for 1H , 125.7 MHz for ^{13}C and 202.4 MHz for ^{31}P , respectively). Chemical shifts are given in ppm from tetramethylsilane as internal standard with $CDCl_3$ as solvent. Chemical shifts in ^{19}F NMR referenced by IUPAC recommendations (2000) and in ^{31}P NMR spectra were referred from external standard—85% H_3PO_4 . The NMR-spectra of the newly synthesized compounds could be found in the Supplementary Materials. Liquid chromatography mass spectrometry analysis (LC-

HRAM) was carried out on Q Exactive[®] hybrid quadrupole-Orbitrap[®] mass spectrometer (ThermoScientific Co, Waltham, MA, USA) equipped with a HESI[®] (heated electrospray ionization) module, TurboFlow[®] Ultra High Performance Liquid Chromatography (UH-PLC) system (ThermoScientific Co, Waltham, MA, USA) and HTC PAL[®] autosampler (CTC Analytics, Zwingen, Switzerland). The chromatographic separations of the analyzed compounds were achieved on Nucleoshell C18 (100 × 2.1 mm, 2.7 μm) analytical column (Macherey-Nagel, Düren, Germany) using gradient elution at 300 μL/min flow rate. The used eluent systems were: A—0.1% formic acid in water; B—0.1% formic acid in CH₃CN. Full-scan mass spectra over the *m/z* range 100–600 were acquired in positive ion mode at resolution settings of 140,000. The used mass spectrometer operating parameters were: spray voltage—4.0 kV; capillary temperature—320 °C; probe heater temperature—300 °C; sheath gas flow rate 40 units; auxiliary gas flow 12 units; sweep gas 2 units (units refer to arbitrary values set by the Q Exactive Tune software); and S-Lens RF level of 50.00. Nitrogen was used for sample nebulization and collision gas in the HCD cell. All derivatives were quantified using 5 ppm mass tolerance filters to their theoretical calculated *m/z* values. Data acquisition and processing were carried out with XCalibur[®] ver 2.4 software package (ThermoScientific Co, Waltham, MA, USA). UV-Vis spectra were carried out on a Shimadzu UV-1800. Fluorescence spectra were recorded at room temperature on a PerkinElmer LS45. Reactions were monitored by TLC on silica gel 60 F₂₅₄. Column chromatography was carried out on silica gel (Merck 0.043–0.063 mm) using as eluent *n*-hexane/EtOAc mixture with increasing polarity. The X-ray data set was collected using a Bruker D8 Venture diffractometer with a microfocus sealed tube and a Photon II detector. Monochromated MoK_α radiation ($\lambda = 0.71073 \text{ \AA}$) was used. Data were collected at 133(2) K and corrected for absorption effects using the multi-scan method. The structure was solved by direct methods using SHELXT [59] and was refined by full matrix least squares calculations on F² (SHELXL2018 [60]) in the graphical user interface Shelxle [61]. Refinement—all non H-atoms were located in the electron density maps and refined anisotropically. C-bound H atoms were placed in positions of optimized geometry and treated as riding atoms. Their isotropic displacement parameters were coupled to the corresponding carrier atoms by a factor of 1.2 (CH, CH₂) or 1.5 (CH₃). Disorder: The ethoxy-group on O4 was split over two positions. Its occupancy factors refined to 0.775 for the major compound.

Computational details—the quantum-chemical calculations of the series of phosphonocoumarins in acetonitrile were performed using density functional theory (DFT) [26–29], time-dependent (TD) DFT [30,31] with Gaussian16 suite of programs [32] and the long range corrected hybrid exchange-correlation functional CAM-B3LYP [35], paired with 6-31++G** basis set was employed and a polarizable continuum model (PCM) was used [36].

All chemical reagents were purchased from Merck and Sigma Aldrich. The starting 6-bromo-3-substituted-2-oxo-2H-1-benzopyrans **5,6,8a,b** were prepared according to reported procedures [38]. The used Pd-complexes (PdCl₂(PPh₃)₂ [62], IMesPd(dmba)Cl [45], and PEPPSI-type catalyst [44]) were prepared according to known procedures.

3.1. Starting Materials

4-Hydroxy-[1,1'-biphenyl]-3-carbaldehyde, **2**

Compound **2** was prepared according to the reported procedure [37].

¹H NMR (500 MHz, CDCl₃) δ = 10.926 (s, 1H, OH), 9.889 (s, 1H, CHO), 7.672–7.781 (m, 2H, aromatic), 7.171–7.573 (m, 5H, aromatic), 7.000 (d, *J* = 8.4 Hz, 1H, aromatic).

Diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate, **5**

Compound **5** was prepared according to the reported procedure [38].

¹H NMR (500 MHz, CDCl₃) δ = 8.425 (d, *J* = 17.1 Hz, 1H, H-4), 7.714–7.728 (m, 2H, H-7, H-5), 7.26 (d, *J* = 9.4 Hz, 1H, H-8), 4.215–4.347 (m, 4H, two CH₃CH₂O), 1.387 (t, *J* = 7.1 Hz, 6H, two CH₃CH₂O).

Ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphinine-3-carboxylate 2-oxide, **6**

Compound **6** was prepared according to the reported procedure [38].

^1H NMR (500 MHz, CDCl_3) δ = 8.132 (d, J = 36.9 Hz, 1H, H-4), 7.604 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H-7), 7.576 (d, J = 2.1 Hz, 1H, H-5), 7.267 (d, J = 8.5 Hz, 1H, H-8), 4.323–4.476 (m, 4H, two CH_2O), 1.412 (t, J = 7.1 Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.391 (t, J = 7.1 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$).

3.2. Procedure for Suzuki Reaction—Preliminary Study

3.2.1. Procedure for Suzuki Reaction with PEPPSI, $\text{Pd}(\text{PPh}_3)_4$, and $\text{IMesPd}(\text{dmba})\text{Cl}$

In a Schlenk tube 0.108 g (0.3 mmol, 1 equiv) of diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate **5**, phenylboronic acid (0.044 g, 0.36 mmol, 1.2 equiv), finely powdered K_2CO_3 (0.124 g, 0.9 mmol, 3 equiv) were placed. A mixture of water:toluene (0.6 mL:2.4 mL), toluene (3 mL), water:dioxane (0.6 mL:2.4 mL), dioxane (3 mL), ethanol:water:toluene (0.5 mL:1 mL:1 mL), or ethanol:water (2 mL:1 mL) were added. The vessel was evacuated under vacuum and refilled with argon four times. After that, the respective catalyst (PEPPSI-type, $\text{Pd}(\text{PPh}_3)_4$, and $\text{IMesPd}(\text{dmba})\text{Cl}$) (3 mol %) was introduced as 0.5 mL THF solution. The resulting suspension was heated at 80 °C for 20 h. After that, the reaction mixture was cooled to room temperature, diluted with CHCl_3 , dried with Na_2SO_4 if water was used, and filtered through a celite pad. Part of the solution (about 3 mL) was evaporated under reduced pressure; the residue was dissolved in CDCl_3 and was analyzed by NMR spectroscopy.

3.2.2. Procedure for Suzuki Reaction with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$

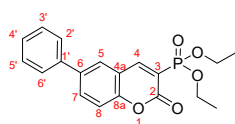
In a Schlenk tube, 0.108 g (0.3 mmol, 1 equiv) of diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate **5**, phenylboronic acid (0.044 g, 0.36 mmol, 1.2 equiv), finely powdered K_2CO_3 (0.124 g, 0.9 mmol, 3 equiv) were placed. A mixture of water:toluene (0.6 mL:2.4 mL), toluene (3 mL), water:dioxane (0.6 mL:2.4 mL), dioxane (3 mL), ethanol:water:toluene (0.5 mL:1 mL:1 mL) or ethanol:water (2 mL:1 mL) were added. After that, the catalyst $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ was introduced as solid, and 0.5 mL of THF were additionally added. The vessel was evacuated under vacuum and refilled with argon four times. The resulting suspension was heated at 80 °C for 20 h. After that, the reaction mixture was cooled to room temperature, diluted with CHCl_3 , dried with Na_2SO_4 if water was used, and filtered through a celite pad. Part of the solution (about 3 mL) was evaporated under reduced pressure. The residue was dissolved in CDCl_3 and was analyzed by NMR spectroscopy.

3.3. General Procedure for the Preparative Suzuki Reaction

In a 50 mL Schlenk flask, a mixture of the respective brominated heterocycle 1.5 mmol (1 equiv), boronic acid 1.8 mmol (1.2 equiv), potassium carbonate 0.622 g (4.5 mmol, 3 equiv), and palladium complex 45 μmol (3 mol%)—29 mg PEPPSI or 32 mg $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, was placed, and the respective solvent was added—3 mL:12 mL water:toluene when a PEPPSI-type catalyst was used, or 15 mL toluene for $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. The flask was evacuated and refilled with argon (four times). The reaction was heated at 80 °C until the coumarin derivative was consumed (TLC-monitoring). The needed time for the reactions is given in Tables 2–4. The reaction was quenched by adding water to the reaction, and the organic layer was extracted with chloroform (5 \times 20 mL). The organic extracts were dried with anhydrous sodium sulfate. After the evaporation of the solvent, the residue was purified by column chromatography using *n*-hexane/EtOAc, *n*-hexane/ CH_2Cl_2 , or *n*-hexane/Et₂O as gradient eluent system.

Diethyl (2-oxo-6-phenyl-2H-chromen-3-yl)phosphonate, **3a**

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate **5** (0.540 g), phenylboronic acid (0.220 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 17 h. The product was purified by column chromatography using *n*-hexane/Et₂O, 0.482 g, 90%, white powder, m.p. = 146.3–149.3 °C. IR (nujol): ν = 1738, 1240, 1052, 1037 cm^{-1} .

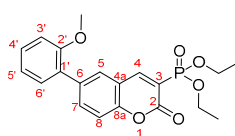


^1H NMR (500 MHz, CDCl_3) δ = 8.509 (d, J = 17.1 Hz, 1H, H-4), 7.780 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H-7), 7.690 (d, J = 2.1 Hz, 1H, H-5), 7.498 (m, 2H, H-4', H-8), 7.413 (m as t, 2H, H-2' and H-6'), 7.337 (m as q, 2H, H-3' and H-5'), 4.153–4.283 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 1.330 (t, J = 7.1 Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (125.7 MHz, CDCl_3) δ = 158.24 (d, J_{CP} = 15.1 Hz, C-2), 154.59 (s, C-8a), 153.46 (d, J_{CP} = 6.5 Hz, C-4), 138.91 (s, C-6), 138.38 (s, C-1'), 133.14 (s, C-7), 129.15 (s, C-2' and C-6'), 128.08 (s, C-5), 127.33 (C-4'), 127.03 (s, C-3' and C-5'), 118.27 (d, J_{CP} = 196.2 Hz, C-3), 118.18 (d, J_{CP} = 14.3 Hz, C-4a), 117.29 (s, C-8), 63.46 (d, J_{CP} = 6.0 Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 16.41 (d, J_{CP} = 6.0 Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) δ = 10.765.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{19}\text{O}_5\text{P}$ [$\text{M}+\text{H}$] $^+$ 359.10429 found 359.10413 (ppm: 0.45).

Diethyl (6-(2-methoxyphenyl)-2-oxo-2H-chromen-3-yl)phosphonate, 3b

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate 5 (0.540 g), 2-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (32 mg) in 15 mL toluene for 48 h. The product was purified by column chromatography using *n*-hexane/ Et_2O , 0.366 g, 63%, yellow slowly solidifying oil. IR (nujol): ν = 1739, 1243, 1056, 1024 cm^{-1} .

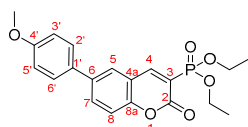


^1H NMR (400 MHz, CDCl_3) δ = 8.556 (d, J = 17.2 Hz, 1H, H-4), 7.805 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.760 (d, J = 2.0 Hz, 1H, H-5), 7.392 (d, J = 8.5 Hz, 1H, H-8), 7.372 (dd, J = 7.5 Hz, 1.1 Hz, 1H, H-3'), 7.308 (dd, J = 5.6 Hz, 1.7 Hz, 1H, H-5'), 7.065 (dd, J = 7.5 Hz, 1.1 Hz, 1H, H-4'), 7.020 (dd, J = 8.3 Hz, 0.7 Hz, 1H, H-6'), 4.203–4.358 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 3.835 (s, 3H, CH_3O), 1.391 (t, J = 7.1 Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) δ = 158.49 (d, J_{CP} = 14.4 Hz, C-2), 156.35 (s, C-8a), 154.25 (s, C-1'), 153.99 (d, J_{CP} = 6.7 Hz, C-4), 135.77 (s, C-7), 135.54 (s, C-2'), 130.57 (s, C-3'), 129.99 (s, C-5'), 129.55 (s, C-5), 128.14 (s, C-6), 121.10 (C-4'), 117.62 (d, J_{CP} = 14.3 Hz, C-4a), 117.51 (d, J_{CP} = 196.2 Hz, C-3), 116.43 (s, C-8), 111.34 (s, C-6'), 63.43 (d, J_{CP} = 6.2 Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 55.54 (s, CH_3O), 16.39 (d, J_{CP} = 6.0 Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) δ = 11.141.

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{21}\text{O}_6\text{P}$ [$\text{M}+\text{H}$] $^+$ 389.11485 found 389.11511 (ppm: -0.67).

Diethyl (6-(4-methoxyphenyl)-2-oxo-2H-chromen-3-yl)phosphonate, 3c

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate 5 (0.540 g), 4-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 48 h. The product was purified by column chromatography using $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 0.551 g, 95%, pale yellow powder, m.p. = 111.6–112.5 $^\circ\text{C}$ IR (nujol): ν = 1740, 1242, 1047, 1025 cm^{-1} .



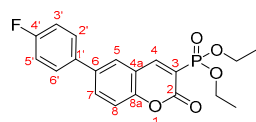
^1H NMR (400 MHz, CDCl_3) δ = 8.494 (d, J = 17.2 Hz, 1H, H-4), 7.739 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.634 (d, J = 2.2 Hz, 1H, H-5), 7.328 (d, J = 8.6 Hz, 1H, H-8), 7.429 (dd, J = 8.8 Hz, 3.1 Hz, 2H, H-3' and H-5'), 6.937 (dd, J = 8.8 Hz, 3.7 Hz, 2H, H-2' and H-6'),

4.137–4.290 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 3.793 (s, 3H, CH_3O), 1.321 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$) 1.319 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 159.73$ (C-4'), 158.31 (d, $J_{\text{CP}} = 14.4$ Hz, C-2), 154.19 (s, C-8a), 153.54 (d, $J_{\text{CP}} = 6.5$ Hz, C-4), 138.03 (s, C-6), 132.78 (s, C-7), 131.35 (s, C-1'), 128.11 (s, C-6' and C-2'), 126.71 (s, C-5), 118.16 (d, $J_{\text{CP}} = 14.3$ Hz, C-4a), 118.10 (d, $J_{\text{CP}} = 196.2$ Hz, C-3), 117.19 (s, C-8), 114.57 (s, C-3' and C-5'), 63.44 (d, $J_{\text{CP}} = 6.0$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 55.42 (s, CH_3O), 16.40 (d, $J_{\text{CP}} = 6.2$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) $\delta = 10.879$.

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{21}\text{O}_6\text{P}$ $[\text{M}+\text{H}]^+$ 389.11485 found 389.11494 (ppm: -0.23).

Diethyl (6-(4-fluorophenyl)-2-oxo-2H-chromen-3-yl)phosphonate, 3d

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate 5 (0.540 g), 4-fluorophenylboronic acid (0.251 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 48 h. The product was purified by column chromatography using CH_2Cl_2 , 0.343 g, 61%, pale yellow powder, m.p. = 115.0–118.2 °C IR (nujol): $\nu = 1734$, 1251, 1057, 1027 cm^{-1} .

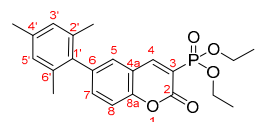


^1H NMR (400 MHz, CDCl_3) $\delta = 8.495$ (d, $J = 17.2$ Hz, 1H, H-4), 7.732 (dd, $J = 8.6$ Hz, 2.2 Hz, 1H, H-7), 7.641 (d, $J = 2.2$ Hz, 1H, H-5), 7.466 (ddq, $J_{\text{HF}} = 8.8$ Hz, 5.0 Hz, $J_{\text{HP}} = 8.8$ Hz, 3.1 Hz, 2H, H-3' and H-5'), 7.356 (d, $J = 8.6$ Hz, 1H, H-8), 7.102 (ddq, $J_{\text{HF}} = 8.6$ Hz, 3.1 Hz, $J_{\text{HP}} = 8.6$ Hz, 3.1 Hz, 2H, H-2' and H-6'), 4.143–4.296 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 1.324 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$) 1.323 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 162.84$ (d, $J_{\text{CF}} = 248.0$ Hz, C-4'), 158.16 (d, $J_{\text{CP}} = 14.4$ Hz, C-2), 154.54 (s, C-8a), 153.26 (d, $J_{\text{CP}} = 6.5$ Hz, C-4), 137.39 (s, C-6), 135.07 (d, $J_{\text{CP}} = 3.3$ Hz, C-1'), 132.94 (s, C-7), 128.71 (d, $J_{\text{CP}} = 10.5$ Hz, C-6' and C-2'), 127.17 (s, C-5), 118.50 (d, $J_{\text{CP}} = 196.7$ Hz, C-3), 118.21 (d, $J_{\text{CP}} = 15.5$ Hz, C-4a), 117.36 (s, C-8), 116.10 (d, $J_{\text{CP}} = 21.7$ Hz, C-3' and C-5'), 63.47 (d, $J_{\text{CP}} = 6.0$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 16.39 (d, $J_{\text{CP}} = 6.0$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{19}F NMR (376.46 MHz, CDCl_3) $\delta = -114.18$; ^{31}P NMR (161.98 MHz, CDCl_3) $\delta = 10.637$.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{FO}_5\text{P}$ $[\text{M}+\text{H}]^+$ 377.09486 found 377.09473 (ppm: 0.34).

Diethyl (6-mesityl-2-oxo-2H-chromen-3-yl)phosphonate, 3e

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate 5 (0.540 g), 2,4,6-trimethylphenylboronic acid (0.294 g), K_2CO_3 (0.622 g) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (32 mg) in 15 mL toluene for 48 h. The product was purified by column chromatography using *n*-hexane/ Et_2O , 0.270 g, 45%, white powder, m.p. = 130.0–132.6 °C. IR (nujol): $\nu = 1744$, 1242, 1053, 1013 cm^{-1} .

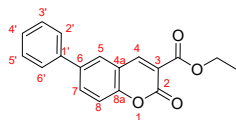


^1H NMR (400 MHz, CDCl_3) $\delta = 8.535$ (d, $J = 17.2$ Hz, 1H, H-4), 7.428 (s, 1H, H-5), 7.425 (s, 1H, H-8), 7.376 (dd as t, $J = 1.5$ Hz, 1H, H-7), 6.972 (d, $J_{\text{HP}} = 0.4$ Hz, 2H, H-3' and H-5'), 4.215–4.367 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 2.345 (s, 3H, CH_3), 1.993 (s, 6H, two CH_3), 1.397 (t, $J = 7.1$ Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 158.34$ (d, $J_{\text{CP}} = 14.2$ Hz, C-2), 154.12 (s, C-8a), 153.58 (d, $J_{\text{CP}} = 6.7$ Hz, C-4), 138.10 (s, C-6), 137.55 (s, C-5), 136.49 (s, C-1'), 135.89 (s, C-6' and C-2'), 135.70 (d, $J_{\text{CF}} = 248.0$ Hz, C-4'), 129.74 (s, C-7), 128.40 (d, $J_{\text{CP}} = 21.7$ Hz, C-3' and C-5'), 118.02 (d, $J_{\text{CP}} = 14.3$ Hz, C-4a), 118.01 (d, $J_{\text{CP}} = 196.1$ Hz, C-3), 116.96 (s, C-8), 63.44 (d, $J_{\text{CP}} = 5.9$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 21.03 (s, CH_3), 20.76 (s, two CH_3), 16.40 (d, $J_{\text{CP}} = 6.3$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) $\delta = 10.984$.

HRMS (ESI) m/z calculated for $C_{22}H_{25}O_5P$ $[M+H]^+$ 401.15124 found 401.15143 (ppm: -0.47).

Ethyl 2-oxo-6-phenyl-2H-chromene-3-carboxylate, 9a

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), phenylboronic acid (0.219 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 30 min. The product was purified by column chromatography using *n*-hexane/ Et_2O and then CH_2Cl_2 , 0.397 g, 90%, pale yellow powder, m.p. = 150.4–151.5 °C. IR (nujol): $\nu = 1758, 1694\text{ cm}^{-1}$.

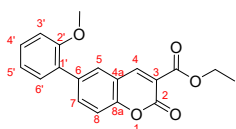


1H NMR (400 MHz, $CDCl_3$) $\delta = 8.510$ (s, 1H, H-4), 7.783 (dd, $J = 10.8$ Hz, 6.4 Hz, 1H, H-7), 7.709 (d, $J = 2.2$ Hz, 1H, H-5), 7.503 (dd as dt, $J = 7$ Hz, 1.5 Hz, 2H, H-2' and H-6'), 7.411 (ddd as dt, $J = 7.4$ Hz, 1.5 Hz, 2H, H-3' and H-5'), 7.352 (d, $J = 8.6$ Hz, 1H, H-8), 7.326 (tt, $J = 7.2$ Hz, 1.3 Hz, 1H, H-4'), 4.356 (q, $J = 7.1$ Hz, 2H, CH_3CH_2O), 1.348 (t, $J = 7.1$ Hz, 3H, CH_3CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 163.06$ (s, \underline{COOEt}), 156.69 (s, C-2), 154.49 (s, C-8a), 148.65 (s, C-4), 138.92 (s, C-6), 138.29 (s, C-1'), 133.29 (s, C-7), 129.14 (s, C-3' and C-5'), 128.07 (s, C-4'), 127.47 (s, C-5), 127.04 (s, C-2' and C-6'), 118.66 (s, C-3), 118.12 (s, C-4a), 117.19 (s, C-8), 62.05 (s, CH_3CH_2O), 14.26 (s, CH_3CH_2O).

HRMS (ESI) m/z calculated for $C_{18}H_{14}O_4$ $[M+H]^+$ 295.09649 found 295.09616 (ppm: 1.12).

Ethyl 6-(2-methoxyphenyl)-2-oxo-2H-chromene-3-carboxylate, 9b

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), 2-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and $Pd(PPh_3)_2Cl_2$ (32 mg) in 15 mL toluene for 24 h. The product was purified by column chromatography using *n*-hexane/ CH_2Cl_2 and then CH_2Cl_2 , 0.331 g, 68%, yellow powder, m.p. = 120.0–124.2 °C. IR (nujol): $\nu = 1773, 1712\text{ cm}^{-1}$.

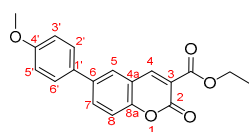


1H NMR (400 MHz, $CDCl_3$) $\delta = 8.566$ (s, 1H, H-4), 7.811 (dd, $J = 8.6$ Hz, 2.2 Hz, 1H, H-7), 7.757 (d, $J = 2.1$ Hz, 1H, H-5), 7.387 (d, $J = 8.6$ Hz, 1H, H-8), 7.374 (td, $J = 5.6$ Hz, 1.7 Hz, 1H, H-5'), 7.313 (td, $J = 7.5$ Hz, 1.7 Hz, 1H, H-3'), 7.064 (td, $J = 7.5$ Hz, 1.1 Hz, 1H, H-4'), 7.020 (dd, $J = 8.3$ Hz, 0.8 Hz, 1H, H-6'), 4.418 (q, $J = 7.1$ Hz, 2H, CH_3CH_2O), 3.834 (s, 3H, CH_3O), 1.421 (t, $J = 7.1$ Hz, 3H, CH_3CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 163.20$ (s, \underline{COOEt}), 156.91 (s, C-2), 156.33 (s, C-1'), 154.15 (s, C-8a), 148.99 (s, C-4), 135.93 (s, C-7), 135.48 (s, C-2'), 130.59 (s, C-3'), 130.05 (s, C-5), 129.54 (s, C-5'), 128.20 (s, C-6), 121.10 (s, C-4'), 118.16 (s, C-3), 118.12 (s, C-4a), 117.58 (s, C-8), 111.34 (s, C-6'), 61.98 (s, CH_3CH_2O), 55.56 (s, CH_3O), 14.26 (s, CH_3CH_2O).

HRMS (ESI) m/z calculated for $C_{19}H_{16}O_5$ $[M+H]^+$ 325.10705 found 325.1069 (ppm: 0.46).

Ethyl 6-(4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxylate, 9c

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), 4-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 45 min. The product was purified by column chromatography using *n*-hexane/ CH_2Cl_2 and then CH_2Cl_2 , 0.444 g, 92%, yellow powder, m.p. = 144.8–146.2 °C. IR (nujol): $\nu = 1761, 1689\text{ cm}^{-1}$.

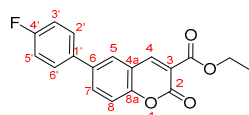


^1H NMR (400 MHz, CDCl_3) δ = 8.572 (s, 1H, H-4), 7.816 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.726 (d, J = 2.2 Hz, 1H, H-5), 7.398 (d, J = 9.3 Hz, 1H, H-8), 7.507 (dq, J = 8.8 Hz, 3.1 Hz, 2H, H-3' and H-5'), 7.009 (dq, J = 8.8 Hz, 3.1 Hz, 2H, H-4' and H-6'), 4.419 (q, J = 7.1 Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 3.867 (s, 3H, CH_3O), 1.422 (t, J = 7.2 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) δ = 163.11 (s, COOEt), 159.72 (s, C-4'), 156.77 (s, C-2), 154.10 (s, C-8a), 148.73 (s, C-4), 137.95 (s, C-6), 132.93 (s, C-7), 131.36 (s, C-1'), 128.10 (s, C-3' and C-5'), 126.83 (s, C-5), 118.54 (s, C-3), 118.10 (s, C-4a), 117.09 (s, C-8), 114.56 (s, C-2' and C-6'), 62.02 (s, $\text{CH}_3\text{CH}_2\text{O}$), 55.42 (s, CH_3O), 14.25 (s, $\text{CH}_3\text{CH}_2\text{O}$).

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{16}\text{O}_5$ $[\text{M}+\text{H}]^+$ 325.10705 found 325.10675 (ppm: 0.92).

Ethyl 6-(4-fluorophenyl)-2-oxo-2H-chromene-3-carboxylate, 9d

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), 4-fluorophenylboronic acid (0.251 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 45 min. The product was purified by column chromatography using CH_2Cl_2 , 0.374 g, 80%, pale yellow powder, m.p. = 180.3–184.7 °C. IR (nujol): ν = 1742, 1711 cm^{-1} .

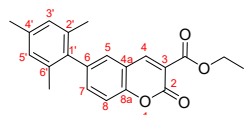


^1H NMR (400 MHz, CDCl_3) δ = 8.577 (s, 1H, H-4), 7.808 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.738 (d, J = 2.2 Hz, 1H, H-5), 7.543 (ddq, J_{HF} = 8.9 Hz, 5.2 Hz; J = 8.9 Hz, 3.2 Hz, 2H, H-3' and H-5'), 7.423 (d, J = 8.6 Hz, 1H, H-8), 7.185 (ddq as tq, J_{HF} = 8.6 Hz, 3.1 Hz; J = 8.6 Hz, 3.1 Hz, 2H, H-2' and H-6'), 4.432 (q, J = 7.1 Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 1.423 (t, J = 7.1 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) δ = 163.02 (s, COOEt), 162.84 (d, J = 248.0 Hz, C-4'), 156.60 (s, C-2), 154.45 (s, C-8a), 148.50 (s, C-4), 137.32 (s, C-6), 135.09 (d, J = 3.2 Hz, C-1'), 133.10 (s, C-7), 128.71 (d, J = 8.2 Hz, C-2' and C-6'), 127.32 (s, C-5), 118.81 (s, C-3), 118.14 (s, C-4a), 117.27 (s, C-8), 116.20 (d, J = 21.7 Hz, C-3' and C-5'), 62.09 (s, $\text{CH}_3\text{CH}_2\text{O}$), 14.24 (s, $\text{CH}_3\text{CH}_2\text{O}$); ^{19}F NMR (376.46 MHz, CDCl_3) δ = -114.196.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{13}\text{FO}_4$ $[\text{M}+\text{H}]^+$ 313.08706 found 313.08682 (ppm: 0.77).

Ethyl 6-mesityl-2-oxo-2H-chromene-3-carboxylate, 9e

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), 2,4,6-trimethylphenylboronic acid (0.294 g), K_2CO_3 (0.622 g) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (32 mg) in 15 mL toluene for 72 h. The product was purified by column chromatography using *n*-hexane/ Et_2O , 0.147 g, 29%, pale yellow powder, m.p. = 142.8–146.2 °C. IR (nujol): ν = 1758, 1691 cm^{-1} .



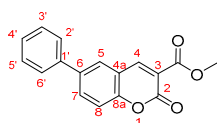
^1H NMR (400 MHz, CDCl_3) δ = 8.518 (s, 1H, H-4), 7.427 (s, 1H, H-8), 7.424 (s, 1H, H-5), 7.386 (dd as t, J = 1.2 Hz, 1H, H-7), 6.968 (d, J = 0.4 Hz, 1H, 2H, H-3' and H-5'), 4.420 (q, J = 7.1 Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 2.343 (s, 3H, CH_3Ar), 1.993 (s, 6H, CH_3Ar), 1.416 (t, J = 7.1 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) 163.16 (s, COOEt), 156.84 (s, C-2), 154.01 (s, C-8a), 148.63 (s, C-4), 138.04 (s, C-6), 137.54 (s, C-5), 136.51 (s, C-1'), 135.91 (s, C-2' and C-6'), 135.79 (s, C-4'), 129.83 (s, C-7), 128.38 (s, C-3' and C-5'), 118.51 (s, C-3), 117.99 (s,

C-4a), 116.95 (s, C-8), 62.02 (s, CH₃CH₂O), 21.04 (s, CH₃Ar), 20.76 (s, two CH₃Ar), 14.26 (s, CH₃CH₂O).

HRMS (ESI) m/z calculated for C₂₁H₂₀O₄ [M+H]⁺ 337.14344 found 337.14352 (ppm: −0.24).

Methyl 2-oxo-6-phenyl-2H-chromene-3-carboxylate, 10a

The product was prepared from methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8b** (0.425 g), phenylboronic acid (0.219 g), K₂CO₃ (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 60 min. The product was purified by column chromatography using *n*-hexane/CH₂Cl₂ and then CH₂Cl₂, 0.409 g, 97%, pale yellow powder, m.p. = 160.7–164.5 °C. IR (nujol): ν = 1755, 1694 cm^{−1}.

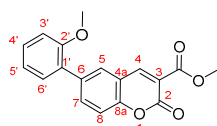


¹H NMR (400 MHz, CDCl₃) δ = 8.627 (s, 1H, H-4), 7.871 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.785 (d, J = 2.2 Hz, 1H, H-5), 7.565–7.589 (m, 2H, H-2' and H-6'), 7.468–7.487 (m, J = 7.4 Hz, 2H, H-3' and H-5'), 7.390–7.432 (m, 1H, H-4'), 7.434 (d, J = 8.8 Hz, 1H, H-8), 3.972 (s, J = 3H, CH₃OOC); ¹³C NMR (100 MHz, CDCl₃) 163.72 (s, COOCH₃), 156.69 (s, C-2), 154.54 (s, C-8a), 149.22 (s, C-4), 138.87 (s, C-6), 138.37 (s, C-1'), 133.45 (s, C-7), 129.15 (s, C-3' and C-5'), 128.09 (s, C-4'), 127.52 (s, C-5), 127.04 (s, C-2' and C-6'), 118.26 (s, C-3), 118.09 (s, C-4a), 117.20 (s, C-8), 52.98 (s, CH₃O).

HRMS (ESI) m/z calculated for C₁₇H₁₂O₄ [M+H]⁺ 281.08084 found 281.08112 (ppm: −1.00).

Methyl 6-(2-methoxyphenyl)-2-oxo-2H-chromene-3-carboxylate, 10b

The product was prepared from methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8b** (0.425 g), 2-methoxyphenylboronic acid (0.273 g), K₂CO₃ (0.622 g) and Pd(PPh₃)₂Cl₂ (32 mg) in 15 mL toluene for 21 h. The product was purified by column chromatography using *n*-hexane/CH₂Cl₂ and then CH₂Cl₂, 0.385 g, 83%, yellow powder, m.p. = 130.9–135.5 °C. IR (nujol): ν = 1760, 1759 cm^{−1}.

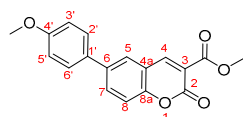


¹H NMR (400 MHz, CDCl₃) δ = 8.611 (s, 1H, H-4), 7.819 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H-7), 7.763 (d, J = 2.1 Hz, 1H, H-5), 7.393 (d, J = 8.8 Hz, 1H, H-8), 7.374 (td, J = 5.6 Hz, 1.7 Hz, 1H, H-5'), 7.311 (dd, J = 7.5 Hz, 1.8 Hz, 1H, H-3'), 7.066 (td, J = 7.5 Hz, 1.0 Hz, H-4'), 7.022 (d, J = 8.3 Hz, H-6'), 3.967 (s, 3H, CH₃OOC), 3.834 (s, 3H, CH₃O); ¹³C NMR (100 MHz, CDCl₃) δ = 163.86 (s, COOCH₃), 156.91 (s, C-2), 154.21 (s, C-8a), 156.32 (s, C-1'), 149.56 (s, C-4), 136.10 (s, C-7), 135.56 (s, C-2'), 130.59 (s, C-5'), 130.11 (s, C-5), 129.57 (s, C-3'), 128.15 (s, C-6), 121.11 (s, C-4'), 117.77 (s, C-3), 117.56 (s, C-4a), 116.33 (s, C-8), 111.34 (s, C-6'), 52.93 (s, CH₃O).

HRMS (ESI) m/z calculated for C₁₈H₁₄O₅ [M+H]⁺ 311.0914 found 311.09083 (ppm: −1.00).

Methyl 6-(4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxylate, 10c

The product was prepared from methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8b** (0.425 g), 4-methoxyphenylboronic acid (0.273 g), K₂CO₃ (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 45 min. The product was purified by column chromatography using *n*-hexane/CH₂Cl₂ and then CH₂Cl₂, 0.463 g, 99%, lemon yellow powder, m.p. = 158.7–161.4 °C. IR (nujol): ν = 1756, 1700 cm^{−1}.

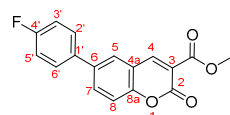


^1H NMR (400 MHz, CDCl_3) δ = 8.613 (s, 1H, H-4), 7.826 (dd, J = 8.6 Hz, 2.6 Hz, 1H, H-7), 7.726 (d, J = 2.2 Hz, 1H, H-5), 7.506 (dq, J = 8.6 Hz, 3.0 Hz, 2H, H-3' and H-5'), 7.403 (d, J = 8.6 Hz, 1H, H-8), 7.011 (dq, J = 8.8 Hz, 3.0 Hz, 2H, H-2' and H-6'), 3.969 (s, J = 3H, CH_3OOC), 3.868 (s, J = 3H, CH_3O); ^{13}C NMR (100 MHz, CDCl_3) δ = 163.77 (s, COOCH_3), 159.75 (s, C-4'), 156.77 (s, C-2), 154.16 (s, C-8a), 149.22 (s, C-4), 138.03 (s, C-6), 133.10 (s, C-7), 131.31 (s, C-1'), 129.15 (s, C-5' and C-3'), 126.89 (s, C-5), 118.07 (s, C-3), 118.15 (s, C-8), 117.12 (s, C-4a), 114.55 (s, C-2' and C-6'), 52.96 (s, CH_3O).

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{14}\text{O}_5$ $[\text{M}+\text{H}]^+$ 311.0914 found 311.09106 (ppm: 1.09).

Methyl 6-(4-fluorophenyl)-2-oxo-2H-chromene-3-carboxylate, 10d

The product was prepared from methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.425 g), 4-fluorophenylboronic acid (0.252 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 60 min. The product was purified by column chromatography using CH_2Cl_2 , 0.443 g, 99%, pale yellow powder, m.p. = 170.8–174.5.7 °C. IR (nujol): ν = 1743, 1712 cm^{-1} .

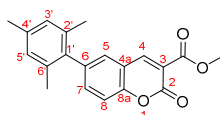


^1H NMR (400 MHz, CDCl_3) δ = 8.618 (s, 1H, H-4), 7.819 (dd, J = 8.6 Hz, 2.2 Hz, 1H, H-7), 7.734 (d, J = 2.2 Hz, 1H, H-5), 7.550 (ddq, J_{HF} = 8.8 Hz, 5.2 Hz; J = 8.8 Hz, 3.1 Hz, 2H, H-3' and H-5'), 7.430 (d, J = 8.6 Hz, 1H, H-8), 7.202 (ddq as tq, J_{HF} = 8.6 Hz, 3.6 Hz; J = 8.6 Hz, 3.2 Hz, 2H, H-2' and H-6'), 3.973 (s, 3H, CH_3OOC); ^{13}C NMR (100 MHz, CDCl_3) δ = 163.68 (s, COOEt), 162.86 (d, J = 248.0 Hz, C-4'), 156.60 (s, C-2), 154.51 (s, C-8a), 149.07 (s, C-4), 137.40 (s, C-6), 135.05 (d, J = 3.3 Hz, C-1'), 133.26 (s, C-7), 128.71 (d, J = 10.5 Hz, C-2' and C-6'), 127.38 (s, C-5), 118.11 (s, C-3), 117.29 (s, C-4a), 118.42 (s, C-8), 116.12 (d, J = 21.7 Hz, C-3' and C-5'), 53.00 (s, CH_3O); ^{19}F NMR (376.46 MHz, CDCl_3) δ = -114.135.

HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{11}\text{FO}_4$ $[\text{M}+\text{H}]^+$ 299.07141 found 299.07090 (ppm: 1.71).

Methyl 6-mesityl-2-oxo-2H-chromene-3-carboxylate, 10e

The product was prepared from methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.425 g), 2,4,6-trimethylphenylboronic acid (0.294 g), K_2CO_3 (0.622 g) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (32 mg) in 15 mL toluene for 90 h. The product was purified by column chromatography using *n*-hexane/ CH_2Cl_2 , 0.085 g, 18%, white powder, m.p. = 139.9–143.5 °C. IR (nujol): ν = 1745, 1706 cm^{-1} .

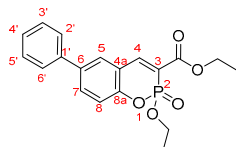


^1H NMR (400 MHz, CDCl_3) δ = 8.564 (s, 1H, H-4), 7.438 (s, 1H, H-8), 7.434 (s, 1H, H-5), 7.392 (dd as t, J = 1.0 Hz, 1H, H-7), 6.970 (d, J = 0.4 Hz, 2H, H-3' and H-5'), 3.968 (s, 3H, CH_3OOC), 2.343 (s, 3H, CH_3Ar), 1.994 (s, 6H, CH_3Ar); ^{13}C NMR (100 MHz, CDCl_3) 163.80 (s, COOEt), 156.84 (s, C-2), 154.07 (s, C-8a), 149.21 (s, C-4), 138.11 (s, C-6), 137.57 (s, C-5), 136.46 (s, C-1'), 135.97 (s, C-2' and C-6'), 137.10 (s, C-4'), 129.90 (s, C-7), 128.39 (s, C-3' and C-5'), 118.57 (s, C-3), 117.96 (s, C-4a), 116.97 (s, C-8), 52.96 (s, CH_3O), 21.04 (s, CH_3Ar), 20.77 (s, two CH_3Ar).

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{18}\text{O}_5$ $[\text{M}+\text{H}]^+$ 323.12779 found 323.12753 (ppm: -0.80).

Ethyl 2-ethoxy-6-phenylbenzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide, 11a

The product was prepared from ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide **6** (0.540 g), phenylboronic acid (0.220 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 16 h. The product was purified by column chromatography using *n*-hexane/ Et_2O , 0.476 g, 89%, pale yellow powder, m.p. = 118.7–120.3 °C. IR (nujol): $\nu = 1715, 1196, 1076, 1028\text{ cm}^{-1}$.

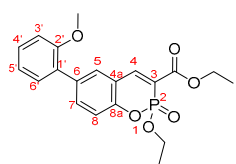


1H NMR (400 MHz, $CDCl_3$) $\delta = 8.307$ (d, $J = 36.9$ Hz, 1H, H-4), 7.702 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H, H-7), 7.657 (d, $J = 2.1$ Hz, 1H, H-5), 7.545 (dq, $J = 7.6$ Hz, 2.0 Hz, 1.5 Hz, 2H, H-2' and H-6'), 7.459 (tt, $J = 2.0$ Hz, 1.5 Hz, 2H, H-3' and H-5'), 7.382 (tt, $J = 7.3, 2.2, 1.3$ Hz, 1H, H-4'), 7.266 (d, $J = 8.5$ Hz, 1H, H-8), 4.413–4.493 (m, 2H, CH_3CH_2OP), 4.323–4.403 (m, 2H, CH_3CH_2OOC), 1.438 (t, $J = 7.0$ Hz, 3H, CH_3CH_2OP), 1.403 (t, $J = 7.1$ Hz, 3H, CH_3CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 163.75$ (d, $J_{CP} = 14.7$ Hz, $COOEt$), 152.01 (d, $J_{CP} = 8.7$ Hz, C-8a), 150.46 (d, $J_{CP} = 3.5$ Hz, C-4), 139.06 (s, C-1'), 137.59 (s, C-6), 132.34 (s, C-7), 129.87 (d, $J_{CP} = 1.5$ Hz, C-5), 127.85 (C-4'), 129.04 (s, C-3' and C-5'), 126.93 (s, C-2' and C-6'), 119.68 (s, C-4a), 119.19 (d, $J_{CP} = 7.5$ Hz, C-8), 118.88 (d, $J_{CP} = 193.3$ Hz, C-3), 64.93 (d, $J_{CP} = 6.3$ Hz, CH_3CH_2OP), 62.04 (s, CH_3CH_2O), 16.47 (d, $J_{CP} = 6.5$ Hz, CH_3CH_2OP), 14.24 (s, CH_3CH_2O); ^{31}P NMR (161.98 MHz, $CDCl_3$) $\delta = 5.321$.

HRMS (ESI) m/z calculated for $C_{19}H_{19}O_5P$ $[M+H]^+$ 359.10429 found 359.10446 (ppm: -0.47).

Ethyl 2-ethoxy-6-(2-methoxyphenyl)benzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide, 11b

The product was prepared from ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide **6** (0.540 g), 2-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and $Pd(PPh_3)_2Cl_2$ (32 mg) in 15 mL toluene for 42 h. The product was purified by column chromatography using *n*-hexane/ $EtOAc$, 0.366 g, 45%, yellow oil. IR (nujol): $\nu = 1700, 1190, 1074, 1035\text{ cm}^{-1}$.

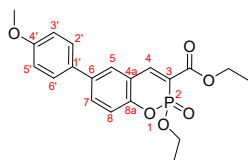


1H NMR (400 MHz, $CDCl_3$) $\delta = 8.284$ (d, $J = 37.0$ Hz, 1H, H-4), 7.651 (dd, $J = 8.6$ Hz, 2.5 Hz, 1H, H-7), 7.636 (s, 1H, H-5), 7.355 (td, $J = 8.0$ Hz, 2.2 Hz, 1H, H-3'), 7.283 (dd, $J = 7.5, 1.7$ Hz, 1H, H-5'), 7.223 (d, $J = 8.2$ Hz, 1H, H-8), 7.023 (td, $J = 7.4, 0.9$ Hz, 1H, H-6'), 6.982 (td, $J = 7.5$ Hz, 1.1 Hz, 1H, H-4'), 4.315–4.487 (m, 4H, CH_3CH_2OP and CH_3CH_2OOC), 3.820 (s, 3H, OCH_3), 1.420 (t, $J = 7.1$ Hz, 3H, CH_3CH_2OP), 1.406 (t, $J = 7.1$ Hz, 3H, CH_3CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 163.89$ (d, $J_{CP} = 13$ Hz, $COOEt$), 156.32 (s, C-1'), 151.63 (d, $J_{CP} = 8.8$ Hz, C-8a), 150.89 (d, $J_{CP} = 3.6$ Hz, C-4), 134.98 (s, C-7), 134.74 (s, C-5), 130.54 (s, C-5'), 129.32 (s, C-3'), 128.36 (s, C-6), 121.04 (s, C-6'), 121.03 (C-4'), 119.18 (d, $J_{CP} = 15.8$ Hz, C-4a), 118.36 (d, $J_{CP} = 7.4$ Hz, C-8), 118.35 (d, $J_{CP} = 177.7$ Hz, C-3), 111.31 (s, C-2'), 64.78 (d, $J_{CP} = 6.4$ Hz, CH_3CH_2OP), 61.98 (s, CH_3CH_2O), 55.56 (s, OCH_3), 16.46 (d, $J_{CP} = 6.5$ Hz, CH_3CH_2OP), 14.24 (s, CH_3CH_2O); ^{31}P NMR (161.98 MHz, $CDCl_3$) $\delta = 5.537$.

HRMS (ESI) m/z calculated for $C_{20}H_{21}O_6P$ $[M+H]^+$ 389.11485 found 389.1149 (ppm: 0.13).

Ethyl 2-ethoxy-6-(4-methoxyphenyl)benzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide, 11c

The product was prepared from ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide **6** (0.540 g), 4-methoxyphenylboronic acid (0.273 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 3 h. The product was purified by column chromatography using *n*-hexane/EtOAc, 0.506 g, 87%, pale yellow powder, m.p. = 132.7–135.3 °C IR (nujol): ν = 1720, 1195, 1043, 1026 cm^{-1} .

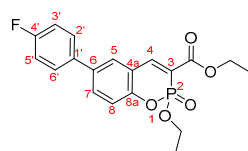


1H NMR (400 MHz, $CDCl_3$) δ = 8.296 (d, J = 36.9 Hz, 1H, H-4), 7.662 (dd, J = 8.6 Hz, 2.0 Hz, 1H, H-7), 7.603 (d, J = 2.3 Hz, 1H, H-5), 7.475 (dq, J = 8.8 Hz, 3.0 Hz, 2H, H-2' and H-6'), 6.989 (dq, J = 8.8 Hz, 3.0 Hz, 2H, H-3' and H-5'), 7.237 (d, J = 8.5 Hz, 1H, H-8), 4.319–4.490 (m, 4H, CH_3CH_2OP and CH_3CH_2OOC), 1.423 (t, J = 7.0 Hz, 3H, CH_3CH_2OP), 1.409 (t, J = 7.1 Hz, 3H, CH_3CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.78 (d, J_{CP} = 13.0 Hz, $COOEt$), 151.58 (d, J_{CP} = 8.6 Hz, C-8a), 150.59 (d, J_{CP} = 3.5 Hz, C-4), 131.55 (s, C-1'), 137.26 (s, C-6), 131.95 (s, C-7), 129.35 (d, J_{CP} = 1.2 Hz, C-5), 159.55 (C-4'), 114.47 (s, C-3' and C-5'), 127.99 (s, C-2' and C-6'), 119.64 (s, C-4a), 119.11 (d, J_{CP} = 7.4 Hz, C-8), 118.66 (d, J_{CP} = 177.3 Hz, C-3), 64.89 (d, J_{CP} = 6.3 Hz, CH_3CH_2OP), 62.02 (s, CH_3CH_2O), 16.47 (d, J_{CP} = 6.4 Hz, CH_3CH_2OP), 14.24 (s, CH_3CH_2O); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ = 5.408.

HRMS (ESI) m/z calculated for $C_{20}H_{21}O_6P$ $[M+H]^+$ 389.11485 found 389.11517 (ppm: −0.82).

Ethyl 2-ethoxy-6-(4-fluorophenyl)benzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide, **11d**

The product was prepared from ethyl 6-bromo-2-ethoxybenzo[e][1,2]oxaphosphinine-3-carboxylate-2-oxide **6** (0.540 g), 4-fluorophenylboronic acid (0.251 g), K_2CO_3 (0.622 g) and PEPPSI (29 mg) in 3 mL:12 mL water:toluene for 2.5 h. The product was purified by column chromatography using *n*-hexane/EtOAc, 0.500 g, 89%, pale yellow powder, m.p. = 115.0–118.2 °C IR (nujol): ν = 1718, 1198, 1078, 1028 cm^{-1} .



1H NMR (400 MHz, $CDCl_3$) δ = 8.294 (d, J = 36.5 Hz, 1H, H-4), 7.647 (dd, J = 8.5 Hz, 2.1 Hz, 1H, H-7), 7.606 (d, J = 2.2 Hz, 1H, H-5), 7.502 (ddq, J = 8.8 Hz, 5.2 Hz, 3.4 Hz, 2H, H-2' and H-6'), 7.149 (tq, J = 8.6 Hz, 3.4 Hz, 2H, H-3' and H-5'), 7.261 (d, J = 8.4 Hz, 1H, H-8), 4.323–4.498 (m, 4H, CH_3CH_2OP and CH_3CH_2OOC), 1.429 (t, J = 7.1 Hz, 3H, CH_3CH_2OP), 1.411 (t, J = 7.1 Hz, 3H, CH_3CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.68 (d, J_{CP} = 13.0 Hz, $COOEt$), 151.98 (d, J_{CP} = 8.6 Hz, C-8a), 150.27 (d, J_{CP} = 3.5 Hz, C-4), 135.23 (d, J = 3.1 Hz C-1'), 136.62 (s, C-6), 132.16 (s, C-7), 129.71 (s, C-5), 162.72 (d, J_{CP} = 247.7 Hz, C-4'), 128.58 (d, J_{CP} = 8.1 Hz, C-3' and C-5'), 115.98 (d, J_{CP} = 21.6 Hz, C-2' and C-6'), 119.88 (s, C-4a), 119.27 (d, J_{CP} = 7.4 Hz, C-8), 118.92 (d, J_{CP} = 162.2 Hz, C-3), 64.98 (d, J_{CP} = 6.3 Hz, CH_3CH_2OP), 62.07 (s, CH_3CH_2O), 16.47 (d, J_{CP} = 6.4 Hz, CH_3CH_2OP), 14.24 (s, CH_3CH_2O); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ = 5.232; ^{19}F NMR (376.46 MHz, $CDCl_3$) δ = −114.590.

HRMS (ESI) m/z calculated for $C_{19}H_{18}FO_5P$ $[M+H]^+$ 377.09486 found 377.09515 (ppm: −0.77).

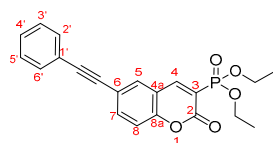
3.4. General Procedure for the Sonogashira Reaction

A mixture of the corresponding coumarin derivative (1.4 mmol), aryl ethyne (1.8 mmol, 1.2 equiv.), $PdCl_2(PPh_3)_2$ /PEPPSI (2 mol%), CuI (4 mol%), Et_3N (3 equiv), and DMF (15 mL) was heated at 80 °C under an Ar atmosphere until the coumarin derivative was consumed

(TLC-monitoring). The needed time for the reactions is given in Table 5. Then, it was concentrated under reduced pressure. The crude product was dissolved in EtOAc, washed several times with brine (5×5 mL), and once with water (1×10 mL). The organic layer was dried with anhydrous sodium. After the evaporation of the solvent, the residue was purified by column chromatography.

Diethyl (2-oxo-6-(phenylethynyl)-2H-chromen-3-yl)phosphonate, 12a

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate **5** (0.500 g), ethynylbenzene (0.170 g), $\text{PdCl}_2(\text{PPh}_3)_2$ (19.4 mg), CuI (10.5 mg), Et_3N (0.58 mL, 0.42 g) and DMF (15 mL) for 20 h. The product was purified by column chromatography using *n*-hexane/EtOAc, 0.437 g, 82%, reddish colored powder, m.p. = 94.3–99.6 °C. IR (nujol): $\nu = 1745, 1239, 1046, 1018 \text{ cm}^{-1}$.

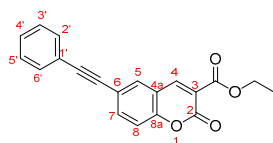


^1H NMR (500 MHz, CDCl_3) $\delta = 8.413$ (d, $J = 17.2$ Hz, 1H, H-4), 7.691 (s, 1H, H-5), 7.674 (s, 1H, H-7), 7.465 (s, 1H, H-8), 7.297 (s, 2H, H-2' and H-6'), 7.271 (s, 2H, H-3' and H-5'), 7.254 (s, 1H, H-4'), 4.146–4.261 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 1.316 (t, $J = 7.1$ Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (125.7 MHz, CDCl_3) $\delta = 157.81$ (d, $J_{\text{CP}} = 14.4$ Hz, C-2), 154.62 (s, C-8a), 152.64 (d, $J_{\text{CP}} = 6.6$ Hz, C-4), 137.06 (s, C-7), 132.07 (s, C-5), 131.67 (s, C-6' and C-2'), 128.83 (s, C-4'), 128.48 (s, C-3' and C-5'), 122.44 (s, C-6), 120.49 (s, C-1'), 118.75 (d, $J_{\text{CP}} = 196.4$ Hz, C-3), 117.99 (d, $J_{\text{CP}} = 14.5$ Hz, C-4a), 117.93 (s, C-8), 90.67 (s, C \equiv C), 87.02 (s, C \equiv C), 63.57 (d, $J_{\text{CP}} = 6.9$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 16.38 (d, $J_{\text{CP}} = 6.3$ Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) $\delta = 10.343$.

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{19}\text{O}_5\text{P}$ $[\text{M}+\text{H}]^+$ 383.10429 found 383.10468 (ppm: -1.02).

Ethyl 2-oxo-6-(phenylethynyl)-2H-chromene-3-carboxylate, 12b

The product was prepared from ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate **8a** (0.444 g), ethynylbenzene (0.184 g), $\text{PdCl}_2(\text{PPh}_3)_2$ (21 mg), CuI (11.4 mg), Et_3N (0.63 mL, 0.46 g) and DMF (15 mL) for 22 h. The product was purified by column chromatography using *n*-hexane/EtOAc, 0.247 g, 52%, reddish colored powder, m.p. = 57.1–61.8 °C. IR (nujol): $\nu = 1744, 1711 \text{ cm}^{-1}$.



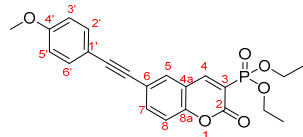
^1H NMR (400 MHz, CDCl_3) $\delta = 8.485$ (s, 1H, H-4), 7.774 (s, 1H, H-5), 7.755 (dd, $J = 7.3$ Hz, 2.0 Hz, 1H, H-7), 7.530–7.555 (m, 2H, H-2' and H-6'), 7.341 (dd, $J = 9.2$ Hz, 0.4 Hz, 1H, H-8), 7.363–7.388 (m, 2H, H-3' and H-5'), 4.421 (q, $J = 7.1$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 1.420 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 162.87$ (s, COOEt), 156.23 (s, C-2), 154.54 (s, C-8a), 147.82 (s, C-4), 122.46 (s, C-6), 120.43 (s, C-1'), 137.19 (s, C-7), 128.49 (s, C-3' and C-5'), 128.83 (s, C-4'), 132.19 (s, C-5), 131.66 (s, C-2' and C-6'), 117.94 (s, C-3), 119.11 (s, C-4a), 117.10 (s, C-8), 62.16 (s, $\text{CH}_3\text{CH}_2\text{O}$), 14.22 (s, $\text{CH}_3\text{CH}_2\text{O}$).

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{14}\text{O}_4$ $[\text{M}+\text{H}]^+$ 319.09649 found 319.09641 (ppm: 0.25).

Diethyl (6-((4-methoxyphenyl)ethynyl)-2-oxo-2H-chromen-3-yl)phosphonate, 12d

The product was prepared from diethyl (6-bromo-2-oxo-2H-chromen-3-yl)phosphonate **5** (0.540 g), 1-ethynyl-4-methoxybenzene (0.238 g), PEPPSI (19.4 mg), CuI (11.4 mg), Et_3N

(0.62 mL, 0.55 g) and DMF (15 mL) for 30 h. The product was purified by column chromatography using *n*-hexane/EtOAc, 0.349 g, 56%, reddish colored powder, m.p. = 131.7–136.0 °C. IR (nujol): ν = 2211, 1744, 1243, 1060, 1027 cm^{-1} .



^1H NMR (400 MHz, CDCl_3) δ = 8.478 (d, J = 17.2 Hz, 1H, H-4), 7.735 (dd, J = 8.5 Hz, 2.0 Hz, 1H, H-7), 7.716 (d, J = 2.0 Hz, 1H, H-5), 7.327 (d, J = 8.5 Hz, 1H, H-8), 7.485 (dq, J = 8.8 Hz, 2.8 Hz, 2H, H-2' and H-6'), 6.901 (dq, J = 8.8 Hz, 2.8 Hz, 2H, H-3' and H-5'), 4.226–4.343 (m, 4H, two $\text{CH}_3\text{CH}_2\text{O}$), 3.844 (s, 3H, CH_3O), 1.392 (t, J = 7.1 Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, CDCl_3) δ = 160.06 (s, C-4'), 157.82 (s, C-2), 154.43 (s, C-8a), 152.69 (d, J_{CP} = 6.6 Hz, C-4), 136.95 (s, C-7), 131.79 (s, C-5), 133.19 (s, C-6' and C-2'), 114.49 (s, C-3' and C-5'), 120.90 (s, C-6), 119.69 (s, C-1'), 118.72 (d, J_{CP} = 196.1 Hz, C-3), 117.98 (d, J_{CP} = 14.5 Hz, C-4a), 117.13 (s, C-8), 90.79 (s, $\text{C}\equiv\text{C}$), 85.83 (s, $\text{C}\equiv\text{C}$), 55.35 (s, CH_3O), 63.54 (d, J_{CP} = 6.0 Hz, two $\text{CH}_3\text{CH}_2\text{O}$), 16.39 (d, J_{CP} = 6.3 Hz, two $\text{CH}_3\text{CH}_2\text{O}$); ^{31}P NMR (161.98 MHz, CDCl_3) δ = 10.390.

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{21}\text{O}_6\text{P}$ $[\text{M}+\text{H}]^+$ 413.11485 found 413.11524 (ppm: −0.94).

4. Conclusions

A synthetic protocol for the efficient preparation of new substituted 3-phosphonocoumarins, 1,2-benzoxaphosphorines, methyl and ethyl coumarin-3-carboxylates via palladium catalyzed cross-coupling reactions was developed. The Suzuki and Sonogashira reaction was applied successfully to obtain the structures in good to quantitative yields.

Quantum-chemical calculations on the spectral properties of aryl and alkynyl 3-phosphonocoumarins were performed as a continuation of our systematic studies on phosphorous-containing coumarin derivatives. It was found that by altering the substituent in C-6, fine tuning of the fluorescent properties could be achieved. Introducing a CH_3O -group in *para*-position in the aryl moiety has the most noticeable effect leading to bathochromic shift in the absorption and fluorescence spectra. This tendency was observed both in the calculated and the experimental data. The photophysical properties of the newly obtained compounds were studied in different solvents. It was found that the type of media has little or no effect on both absorption and fluorescence maxima. The experimental data are in good agreement with the theoretically predicted photophysical properties of the compounds.

Supplementary Materials: Crystallographic data for the structures in this paper have been deposited in the Cambridge Crystallographic Data Center as a supplementary publication (**3a**, CCDC 2209998). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, U.K [Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk. The Supplemental Material file of CCDC includes the CIF file of **3a**. The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27217649/s1>, NMR spectroscopy data and X-ray analysis.

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