



An appraisal of the Suzuki cross-coupling reaction for the synthesis of novel fluorescent coumarin derivatives



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ABSTRACT

We report the chemical design and development of 3-aryl-substituted 7-alkoxy-4-methylcoumarins with enhanced fluorogenic properties. The 3-aryl substituents are installed via an optimized Suzuki–Miyaura cross-coupling (SMC) reaction between a 7-alkoxy-3-bromo-4-methylcoumarin and aryl boronic MIDA esters using Pd(OAc)₂/XPhos in a catalytic system with K₂CO₃ in aqueous THF. Under these conditions, an exocyclic ester functionality is found to be unaffected. Subsequent saponification revealed a carboxylic acid functionality that is suitable for conjugation reactions. Evaluation of their fluorescence properties indicated that the installed 3-heteroaryl substituent, particularly benzofuran-2-yl, resulted in a significant red shift of both the excitation and emission wavelengths.

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Fluorescence bio-imaging has widespread uses in biochemical and cellular research. In this context, fluorescent probes, such as tagged or labeled biomolecules are indispensable tools for monitoring molecular changes continuously in the intracellular environment at low concentrations.¹ In the selection of a suitable fluorogenic tag, the fluorophore should have a number of desired characteristics, including chemical and photo-stability, a high quantum yield, a large Stokes' shift, good solubility under physiological conditions, and low cell toxicity. For example, high fluorescent quantum yields are important to reduce (i) the concentration of the probe, which in turn minimizes potential toxicity, and (ii) interference from endogenous components of the cells.²

In this regard, coumarin derivatives have many of the important desirable features, including small size, easy to manipulate synthetically, low toxicity, large Stokes' shifts to avoid a significant overlap of the excitation and emission spectra, and good photo-stability.^{3–5}

Coumarin derivatives are already used as fluorescent sensors for Mg²⁺,⁶ Hg²⁺,⁷ and cytochrome P450 function.⁸ A typical feature of the fluorogenic coumarin moiety is the presence of an electron-donating group at the 7-position. However, a limitation of fluorogenic coumarin derivatives when used for bio-imaging is the interference of background fluorescence from components of the cells, primarily due to the short excitation wavelength of coumarin in the UV region.⁹ In order to address this limitation, both the

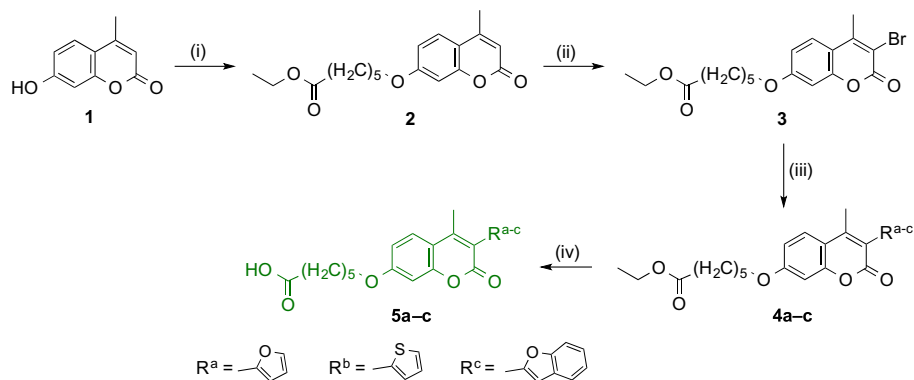
absorption and emission maxima of coumarin could be shifted to longer wavelengths by installing a heteroaromatic substituent at the 3-position, which effectively extends the π system of the coumarin moiety.⁹ We¹⁰ and others^{4,11} have adopted this approach; for example, the Bauerle and Wang groups confirmed that the fluorescence intensity was enhanced by modification of the parent coumarin at the 3-position.^{4f,11}

Thus, in order to exploit many of the unique features of fluorogenic coumarin, we have designed and synthesized a panel of multifunctional coumarin tags, 6-[(3-aryl-4-methylcoumarin-7-yl)oxy]hexanoic acids, which are capable of conjugation reactions with substrates via, for example, amide bond formation. The fluorogenic properties of our coumarin tags are enhanced by the unique heteroaryl substituent at the C3-position. We report, for the first time, an extensive appraisal of the Pd(0)-catalyzed Suzuki–Miyaura cross-coupling (SMC) reaction conditions for the installation of the desired heteroaryl substituent.

Thus, the desired intermediate ethyl 6-[(3-bromo-4-methylcoumarin-7-yl)oxy]hexanoate (**3**) was obtained from 7-hydroxy-4-methylcoumarin (**1**) in two steps (Scheme 1). In the first step, the alkylation of the phenolic group with ethyl 6-bromohexanoate was carried out in DMF at 75 °C for 4 h, which gave the product **2** in 85% yield. Since aryl bromides and iodides are often used in SMC reactions due to their high reactivity, by facilitating the oxidative addition step in the SMC catalytic cycle,¹² we next considered regioselective bromination of our intermediate **2**. Direct bromination of aromatic compounds using bromine generates toxic and corrosive HBr, which is hazardous to the environment;¹³ the reaction

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Scheme 1. Synthesis of fluorescent 7-alkoxy-3-aryl-4-methylcoumarin derivatives. Reagents and conditions: (i) ethyl 6-bromohexanoate, K_2CO_3 , DMF, 75 °C; (ii) NBS, NH_4OAc ; (iii) catalyst/ligand, base, 60–70 °C; (iv) LiOH, 5 equiv, THF– H_2O (3:2).

is also generally non-selective, forming mixtures of mono- and polybrominated products.¹⁴ *N*-Bromosuccinimide (NBS) is considered a superior brominating agent due to the ease of its handling and low cost.¹³ Thus, treatment of intermediate **2** with NBS, in the presence of NH_4OAc , for 30 min at ambient temperature afforded **3** in excellent yield (85%).

Next, Pd(0)-catalyzed cross-coupling of intermediate **3** with various heteroaryl boronic esters was evaluated. In order to gauge the potential of established SMC methodologies, 2-furan boronic acid was used as a model coupling substrate. Among the various reported SMC reaction conditions, Pd(dppf)₂ as catalyst and K_2CO_3 as the base suspended in 1,4-dioxane are considered highly efficient in cross-coupling conjugation of aryl halides with various boronic compounds.^{12c} Therefore, this protocol was applied to our coumarin scaffold **3**.

Initially, when coumarin **3** was allowed to react with 1.5 equiv of furan boronic acid at 70 °C for 24 h, the 3-furyl product **4a** was obtained in trace amounts (Table 1, entry 1), with near complete recovery of the starting material **3**. Although an increase in the boronic acid quantity (2 equiv) improved the reaction, the conversion was still poor (Table 1, entry 2). This inefficiency was attributed to the instability of the substrate 2-furan boronic acid, since it is known to decompose via protodeboronation.¹⁵ Moreover, the protodeboronation is thought to be accelerated by heat in the presence of a base.¹⁵ However, decreasing the quantities of the base to

one equivalent did not improve the conversion (Table 1, entry 3). To overcome this problem, 2-furan boronic MIDA ester was used since it is considered to be more stable than the corresponding boronic acid.¹⁵ Although the reaction was slow and did not reach completion (Table 1, entry 4), it gave an improved and consistent result. Consequently, furan MIDA ester was used in subsequent evaluation of the SMC reaction.

The role of the base in SMC reactions is thought to accelerate the transmetallation rate through the coordination of a negatively charged base to the boron atom and to increase its nucleophilicity for transmetallation.^{12c,16} The bases most commonly employed for SMC are K_3PO_4 , Na_2CO_3 , and K_2CO_3 . Others, including LiOH, KOH, and KF have also been used.¹⁷ The base can be used in aqueous solution or as a suspension in 1,4-dioxane or DMF.^{16b} At present, the choice of base is still empirical and no general rule for their selection has been established. In our system, changing the base to an organic base, for example, triethylamine and *N*-methylmorpholine (NMM) afforded the coupled product **4a** in trace amounts (Table 1, entries 5 and 6).

Cesium base compounds are known to be superior to their potassium analogues with respect to reaction time and yield.¹⁸ Litke and et al. used Cs_2CO_3 and found that the coupling reaction was more rapid in the presence of cesium compounds.^{12b} Hence, by changing the base to Cs_2CO_3 , the progress of our SMC reaction improved to 35%, but the conversion was still incomplete (Table 1,

Table 1
Optimized Pd-catalyzed Suzuki cross-coupling reactions of ethyl 6-[(3-bromo-4-methylcoumarin-7-yl)oxy]hexanoate (**3**) with boronic acid or MIDA esters

Entry	Aryl boronic acid or ester (2 equiv)	Catalytic system	Base (3 equiv)	Solvent	Time (h)	Conversion rate ^a (%)
1	2-Furan boronic acid ^b	PdCl ₂ (dppf)	K_2CO_3	1,4-Dioxane	24	<0.2
2	2-Furan boronic acid	PdCl ₂ (dppf)	K_2CO_3	1,4-Dioxane	30	19
3	2-Furan boronic acid	PdCl ₂ (dppf)	$K_2CO_3^c$	1,4-Dioxane	26	2
4	2-Furan boronic MIDA	PdCl ₂ (dppf)	K_2CO_3	1,4-Dioxane	30	22
5	2-Furan boronic MIDA	PdCl ₂ (dppf)	Et_3N	1,4-Dioxane	24	2
6	2-Furan boronic MIDA	PdCl ₂ (dppf)	NMM	1,4-Dioxane	26	<0.2
7	2-Furan boronic MIDA	PdCl ₂ (dppf)	Cs_2CO_3	1,4-Dioxane	24	35
8	2-Furan boronic MIDA	PdCl ₂ (dppf)	K_2CO_3	1,4-Dioxane/ H_2O	20	71
9	2-Furan boronic MIDA	PdCl ₂ (dppf)	Et_3N	1,4-Dioxane/ H_2O	23	9
10	2-Furan boronic MIDA	PdCl ₂ (dppf)	NMM	1,4-Dioxane/ H_2O	24	<0.2
11	2-Furan boronic MIDA	PdCl ₂ (dppf)	K_2CO_3 /TBAB	1,4-Dioxane/ H_2O	22	46
12	2-Furan boronic MIDA	PdCl ₂ (dppf)	K_2CO_3	DMF/ H_2O	24	<0.2
13	2-Furan boronic MIDA	PdCl ₂ (dppf)	K_2CO_3	THF/ H_2O	5	71
14	2-Furan boronic MIDA	Pd(PPH_3) ₄	K_2CO_3	THF/ H_2O	23	58
15	2-Furan boronic MIDA	Pd(OAc) ₂ /P(Ph) ₃	K_2CO_3	THF/ H_2O	22	48
16	2-Furan boronic MIDA	Pd(OAc) ₂ /XPhos	K_2CO_3	THF/ H_2O	2.5	71
17	2-Thiophene boronic MIDA	Pd(OAc) ₂ /XPhos	K_2CO_3	THF/ H_2O	4	76
18	2-Benzo[b]furan boronic MIDA	Pd(OAc) ₂ /XPhos	K_2CO_3	THF/ H_2O	4	90

^a Conversion rate is based on a combination of isolated yields (following a simple work-up) and purity determined by ¹H NMR and RP-HPLC.

^b 1.5 equiv.

^c 1.0 equiv.

entry 7). The use of an aqueous base solution was then investigated. By using 0.75 M K_2CO_3 in H_2O , introduction of the furan at the 3-position occurred in a good yield. Unfortunately, the reaction was still incomplete, and we were concerned with possible saponification side-reactions. In fact, according to 1H NMR analysis, the purity of the product was >90% (Table 1, entry 8). The use of H_2O with the organic bases, Et_3N and NMM did not change the efficiency of the reaction (Table 1 entries 9 and 10), and was observed to be detrimental. Therefore, the role of H_2O appeared to enhance the solubility of K_2CO_3 . Moreover, it was reported that tetra-*n*-butylammonium bromide (TBAB), a phase-transfer reagent, may improve the yields of SMC reactions in water by enhancing the solubility of the organic substrates in the solvent mixture.¹⁹ However, in our hands, the addition of TBAB (dissolved in water) did not enhance the reaction outcome (Table 1, entry 11).

In order to study the effect of solvents on our system, the reaction was carried out in aqueous mixtures of 1,4-dioxane, DMF, and THF. The use of aqueous THF appeared to be the most appropriate, as was evident from the quicker (5 h reaction time) conversion rate (Table 1, compare entries 8, 12 and 13). Unexpectedly, the use of aqueous DMF was found to be detrimental, resulting in only trace amounts of the desired product **4a**.

Apart from solvents and bases, the catalyst itself plays an important role in SMC reactions.²⁰ Thus, with the solvent (aqueous THF) and base (K_2CO_3) selected, catalyst screening was then performed. Among different ligand systems, phosphine-based ligands, such as trialkylphosphine and electron-rich dialkylbiarylphosphines, have emerged as being effective for SMC reactions.²⁰ The use of $PdCl_2(dppf)$ has been reported by Molander and Yun²¹ as an efficient catalyst for the specific cross-coupling of coumarin bromide with a MIDA boronic ester. Similarly, in our system, the conversion was observed to be efficient (Table 1, entry 13). However, changing the catalytic system to $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ gave disappointing results (Table 1, entries 14 and 15), in which the observed conversion was reduced from ca. 70% to 50–60%.

Gratifyingly, the use of the catalytic system $Pd(OAc)_2/XPhos$ furnished the cross-coupled product **4a** with high conversion after 2.5 h (Table 1, entry 16). A careful analysis of the reaction optimization results showed that the catalytic system $Pd(OAc)_2/XPhos$ with K_2CO_3 in aqueous THF proved to be the most appropriate reaction conditions, affording an excellent yield of 76% and purity (established using RP-HPLC) of 93%.

In order to assess the reliability of the optimized SMC conditions, two other boronic MIDA esters, 2-thiophene boronic MIDA ester and 2-benzo[*b*]furan boronic MIDA ester were reacted with coumarin intermediate **3**. The results confirmed the superiority of the optimized SMC conditions, in which the products **4b** and **4c**²² were obtained in high yields within four hours (Table 1, entries 17 and 18).

The last step was saponification of **4a–c** to afford coumarin reagents **5a–c**. The aqueous base LiOH was chosen, and reactions were performed at ambient temperature in THF– H_2O , 3:2 for 1.5–2.5 h to afford pale yellow products in good yields (64–73%).

The new derivatives **5a–c** were then evaluated for their spectroscopic properties under near physiological conditions (20 mM HEPES buffer at pH 7). Interestingly, all the newly synthesized coumarin derivatives **5a–c** are characterized by a higher molar extinction (ϵ) at λ_{max} when compared to the C3-unsubstituted reagent **5** ($R = H$) by ca. twofold (Table 2). Furthermore, the installed 3-aryl substituent resulted in a significant bathochromic shift of both the absorption maximum λ_{max} and emission maximum λ_{em} . Thus, compared to **5**, the shifts in (λ_{ex}) and (λ_{em}) were found to be 5–20 nm and 71–100 nm, respectively, (Table 2 and Fig. 1).

Expectedly, all the newly synthesized coumarin derivatives **5a–c** showed significantly large Stokes' shifts (121–135 nm), which is

Table 2

Photophysical properties (λ in nm and ϵ in $mol^{-1} L cm^{-1}$) of the coumarin **5** and the 3-aryl coumarin derivatives **5a–c**

Compound	λ_{max}	λ_{ex}	λ_{em}	ϵ
5 [*]	320	324	380	9709
5a	345	345	475	18,810
5b	335	330	451	16,110
5c	345	345	480	17,060

^{*} Compound **5** is 6-[(4-methylcoumarin-7-yl)oxy]hexanoic acid.

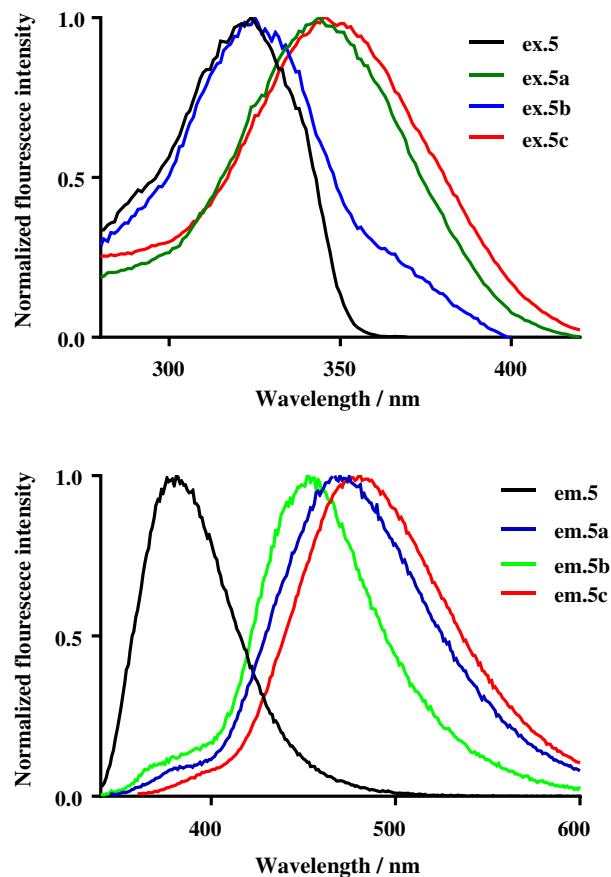


Figure 1. Normalized excitation (top) and emission (bottom) spectra of solutions of **5** and **5a–c**. The measurements were carried out in HEPES buffer.

highly desirable since this allows easy discrimination of excitation and emission wavelengths.

In summary, we have undertaken a thorough evaluation of SMC conditions for the cross-coupling of a modified 3-bromocoumarin with aryl boronic acid derivatives. We established that the recently reported aryl boronic MIDA esters^{15a} are best suited for this type of challenging SMC reaction, and that the optimal conditions involved the use of $Pd(OAc)_2/XPhos$ as the catalytic system and K_2CO_3 in aqueous THF as the base. Under these conditions, SMC reactions performed at 60–70 °C were completed within 2.5–4 h. Moreover, our 3-heteroaryl-modified coumarin derivatives displayed enhanced fluorogenic properties. For example, the 3-benzo[*b*]furan-2-yl coumarin derivative **5c**, when excited at 345 nm, emits blue-green fluorescence. Given these unique features, together with the strategically placed 6-carboxyhexyloxy group (at the C7-position), we anticipate these new coumarin derivatives will be useful reagents for the labeling/tagging of bio(macro)molecules for chemical biology studies.

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Supplementary data

Supplementary data (a detailed account of the optimized experimental procedures for the chemical synthesis of compounds **2**, **3**, **4a–c**, and **5a–c** and their physicochemical characterization, as well as spectrophotometric analysis of the modified coumarin derivatives **5a–c** performed in HEPES buffer 20 mM, pH 7) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.08.058>.

References and notes

- (a) De Silva, A. P.; Gunaratne, H. Q.; Gunnlaugsson, T.; Huxley, A. J.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515; (b) Lackowitz, J. R. *Principles of Fluorescence Spectroscopy*; Springer Science: New York, 2006.
- Chan, J.; Dodani, S. C.; Chang, C. J. *Nat. Chem.* **2012**, *4*, 973.
- (a) Le Droumaguet, C.; Wang, C.; Wang, Q. *Chem. Soc. Rev.* **2010**, *39*, 1233; (b) Drexhage, K. H. *Dye Lasers In*; Springer-Verlag: Berlin, 1973; Vol. 1, p 161; (c) Park, S. Y.; Ebihara, M.; Kubota, Y.; Funabiki, K.; Matsui, M. *Dyes Pigments* **2009**, *258*.
- (a) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059; (b) Lim, N. C.; Bruckner, C. *Chem. Commun.* **2004**, 1094; (c) Lim, N. C.; Schuster, J. V.; Porto, M. C.; Tanudra, M. A.; Yao, L.; Freake, H. C.; Bruckner, C. *Inorg. Chem.* **2005**, *44*, 2018; (d) Katerinopoulos, H. E. *Curr. Pharm. Des.* **2004**, *10*, 3835; (e) Hirano, T.; Hiromoto, K.; Kagechika, H. *Org. Lett.* **2007**, *9*, 1315; (f) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603; (g) Welser, K.; Perera, M. D.; Aylott, J. W.; Chan, W. C. *Chem. Commun.* **2009**, 6601.
- (a) Liu, X.; Cole, J. M.; Waddell, P. G.; Lin, T. C.; Radia, J.; Zeidler, A. J. *Phys. Chem. A* **2012**, *116*, 727; (b) Lambert, J. B. *Introduction to Organic Spectroscopy*; Macmillan: New York, 1987. p 454.
- Ray, D.; Bharadwaj, P. K. *Inorg. Chem.* **2008**, *47*, 2252.
- Shiraishi, Y.; Sumiya, S.; Hirai, T. *Org. Biomol. Chem.* **2010**, *8*, 1310.
- Onderwater, R. C. A.; Venhorst, J.; Commandeur, J. N. M.; Vermeulen, N. P. E. *Chem. Res. Toxicol.* **1999**, *12*, 555.
- Sawa, M.; Hsu, T. L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C. H. *Proc. Nat. Acad. Sci. U.S.A.* **2006**, *103*, 12371.
- Welser, K.; Grilj, J.; Vauthey, E.; Aylott, J. W.; Chan, W. C. *Chem. Commun.* **2009**, 671.
- Schiedel, M. S.; Briehn, C. A.; Bauerle, P. *Angew. Chem.* **2001**, *40*, 4677.
- (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020; (c) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
- Das, B.; Venkateswarlu, K.; Majhi, A.; Siddaiah, V.; Reddy, K. R. *J. Mol. Catal. A-Chem.* **2007**, *267*, 30.
- Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693.
- (a) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961; (b) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130; (c) Woerly, E. M.; Miller, J. E.; Burke, M. D. *Tetrahedron* **2013**, *69*, 7732; (d) Miyaura, N. *Cross-Coupling Reactions*; Springer: Berlin Heidelberg, 2002. p 48; Due to their good stability and ability for in situ slow release of the corresponding boronic acids, the aryl boronic *N*-methyliminodiacetic acid (MIDA) esters have been used for tandem C–C cross-coupling reactions. For a review article, see: (e) Gillis, E. P.; Burke, M. D. *Aldrichim. Acta* **2009**, *42*, 17.
- (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461; (b) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
- Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
- Hüber, M. M. *Acros Org. Acta* **1998**, *7*.
- Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
- Das, P.; Bora, U.; Tairai, A.; Sharma, C. *Tetrahedron Lett.* **2010**, *51*, 1479.
- Molander, G. A.; Yun, C.-S. *Tetrahedron* **2002**, *58*, 1465.
- An optimized procedure for the SMC reaction to yield ethyl 6-[(3-benzo[*b*]furan-2-yl)-4-methylcoumarin-7-yl]oxy]hexanoate (**4c**). To a solution of ethyl 6-[(3-bromo-4-methylcoumarin-7-yl)oxy]hexanoate (**3**) (200 mg, 0.504 mmol) in THF (10 mL) was added the catalyst Pd(OAc)₂ (5.66 mg, 0.0252 mmol, 0.05 equiv) and XPhos (24.05 mg, 0.0504 mmol, 0.1 equiv). The resulting yellow solution was degassed, followed by the sequential addition of K₂CO₃ (153.17 mg, 1.513 mmol, 3.0 equiv) in H₂O (0.5 mL) and 2-benzofuran boronic MIDA ester. The mixture was stirred in dark at 60 °C for 3 h under N₂ atmosphere and monitored by TLC (CH₃Ph–EtOAc, 95:5; R_f = 0.37). After allowing the mixture to cool to ambient temperature, the solvent was removed in vacuo. The residual material was dissolved in CHCl₃ (30 mL), filtered under gravity, and the filtrate was extracted with aqueous NaHCO₃ (30 mL), aqueous KHSO₄ (30 mL), and brine (2 × 30 mL). The organic extract was dried (MgSO₄) and evaporated to dryness in vacuo to afford **4c** as a yellow solid (210 mg, 96%). Mp 100–102 °C. ES-MS *m/z* found 435.1415 (MH⁺), calcd. 435.1808. ¹H NMR (δ, [d₆]-DMSO, 400 MHz) 7.87 (d, *J* = 9 Hz, 1H, C₅-H coumarin), 7.71 (dd, *J*₁ = 7 Hz, *J*₂ = 0.8 Hz, 1H, benzofuran-yl-H), 7.62 (dd, *J*₁ = 7.3 Hz, *J*₂ = 0.8 Hz, 1H, benzofuran-yl-H), 7.36 (td, *J*₁ = 6.9 Hz, *J*₂ = 1.5 Hz, 1H, benzofuran-yl-H), 7.29 (td, *J*₁ = 6.5 Hz, *J*₂ = 1 Hz, 1H, benzofuran-yl-H), 7.20 (d, *J* = 0.8 Hz, 1H, benzofuran-yl-H), 7.04 (dd, *J*₁ = 4.1 Hz, *J*₂ = 2.5 Hz, 1H, C₆-H coumarin), 7.01 (d, *J* = 2.5 Hz, 1H, C₈-H coumarin), 4.11 (t, *J* = 6.6 Hz, 2H, CH₂CH₂O), 4.05 (q, *J*₁ = 14.3 Hz, *J*₂ = 7.1 Hz, 2H, CH₂CH₃), 2.55 (s, 3H, C₄-CH₃ coumarin), 2.30 (t, *J* = 6.7 Hz, 2H, CH₂CO₂Et), 1.79–1.73 (m, 2H, CH₂CH₂O), 1.64–1.56 (m, 2H, CH₂CH₂CO₂Et), 1.48–1.40 (m, 2H, CH₂CH₂CO₂Et), 1.17 (t, *J* = 7.5 Hz, 3H, CH₃CH₂). ¹³C NMR (δ, [d₆]-DMSO, 100 MHz): 172.81, 162.38, 158.69, 154.05, 152.16, 149.58, 127.96, 127.61, 124.76, 123.06, 121.72, 121.32, 113.05, 111.10, 109.14, 104.21, 100.92, 68.27, 59.66, 33.42, 28.10, 24.94, 24.17, 16.72, 14.12.