Synthesis of 4-Substituted Coumarins via the Palladium-Catalyzed Cross-Couplings of 4-Tosylcoumarins with Terminal Acetylenes and Organozinc Reagents

Jie Wu, Yun Liao, and Zhen Yang*

Institute of Chemistry and Cell Biology, Harvard Medical School, 250 Longwood Avenue, SGM 604, Boston, Massachusetts 02115-5731

zhen_yang@hms.harvard.edu

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Coumarin is an important class of benzopyrones that is found in nature and acts as a structural subunit of more complex natural products.[1] These molecules generally have a broad range of biological activities.[2] For example, Novobiocin **1** (Figure 1) is a coumarin-derived antibiotic which acts as a competitive inhibitor of the bacterial ATP binding gyrase B subunit, blocking negative supercoiling of relaxed DNA;[2a,d,g] Wedelolactone **2** is a naturally occurring product, which is used as a venomous snake-bite antidote.[2e] Coumarin is also widely used for flash pumpable laser dyes or for the photographic purposes because its triplet excited-state often occurs in high yield.[3]

During the development of a chemical genetic approach of analyzing biological systems by using small molecules

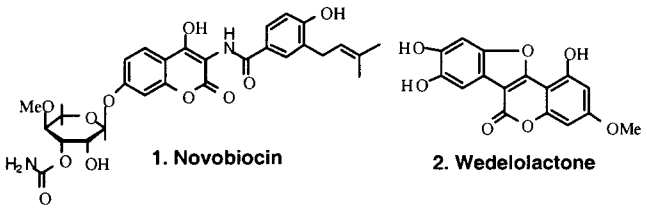

Figure 1. Coumarin-based biological active compounds.

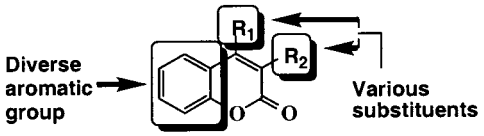

Figure 2. Diversity-based coumarin scaffold.

in an appropriate cell-based assay,[4] we became interested in the synthesis of a combinatorial library based on the scaffold of coumarin. Our library model is shown in Figure 2, which includes three centers for introduction of diversity into coumarin molecule.

We therefore, initiated a program to develop the corresponding methods for generating a coumarin library, which includes developing a novel synthetic method to construct 4-hydroxycoumarin scaffolds, and attaching diversified R_1 and R_2 to the coumarin scaffolds.

We describe herein our recent studies of the palladium-catalyzed carbon−carbon bond formation between 4-tosylcoumarins and terminal acetylenes to generate 4-alkynylcoumarin. To the best of our knowledge, this demonstration represents the first example of arenesulfonates coupling with terminal acetylenes under Sonogashira reaction conditions.

Taking into consideration the synthetic potentials of alkynyl fragments for a library construction, we wanted to attach diverse alkynyl groups at the C-4 position of coumarins (Scheme 1). We believed that these conjugated enynes **4** could be further utilized as precursors to construct even more complex molecules.[5] Since many terminal acetylenes are commercially available or synthetically accessible, this design may be applicable to generate a large number of coumarin-based molecules.

The Sonogashira reaction[6] (the Pd^0/Cu^I-catalyzed coupling of aryl or vinyl halides/triflates with terminal acetylenes under basic conditions) is a versatile method for the carbon−carbon bond formation and has been widely applied in diverse areas of chemistry. However, the instability of vinyl triflates[7] [**3** in Scheme 1, $X = SO_2CF_3$] prevents us from using them in the Sonagashira

(1) (a) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59−62. (b) Maier, W.; Schmidt, J.; Nimtz, M.; Wray, V.; Strack, D. *Phytochemistry* **2000**, *54*, 473−479. (c) Garcia-Argaez, A. N.; Ramirez Apan, T. O.; Delgado, H. P.; Velazquez, G.; Martinez-Vazquez, M. *Planta Med.* **2000**, *66*, 279−281. (d) Zhou, P.; Takaishi, Y.; Duan, H.; Chen, B.; Honda, G.; Itoh, M.; Takeda, Y.; Kodzhimatov, O. K.; Lee, K.-H. *Phytochemistry* **2000**, *53*, 689−697. (e) Khalmuradov, M. A.; Saidkhodzhaev, A. I. *Chem. Nat. Compd.* **1999**, *35*, 364. (f) Kamalam, M.; Jegadeesan, M. *Indian Drugs* **1999**, *36*, 484−486. (g) Tan, R. X.; Lu, H.; Wolfender, J. L.; Yu. T. T. Zheng, W. F.; Yang, L.; Gafner, S.; Hostettmann, K. *Planta Med.* **1999**, *65*, 64−67. (h) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97−109. (I) Bal-Tembe, S.; Joshi, D. D.; Lakdawala, A. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1996**, *35B*, 518. (j) Silvan, A. M.; Abad, M. J.; Bermejo, P.; Villar, A.; Sollhuber, M. *J. Nat. Prod.* **1996**, *59*, 1183. (k) Yang, Y. M.; Hyun, J. W.; Sung, M. S.; Chung, H. S.; Kim, B. K.; Paik, W. H.; Kang, S. S.; Park, J. G. *Planta Med.* **1996**, *62*, 353. (l) Pereira, N. A.; Pereira, B. M. R.; Celia do Nascimento. M.; Parente, J. P.; Mors, W. B. *Planta Med.* **1994**, *60*, 99−100.

(2) (a) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474, 4478. (b) Murray, R. D. H.; Méndez, J.; Brown, S. A. *The natural coumarines: Occurrence, Chemistry, and Biochemistry*; Wiley: New York, 1982. (c) Ali, J. A.; Jackson, A. P.; Howells, A. J.; Maxwell, A. *Biochemistry* **1993**, *32*, 2717−2724. (d) Pereira, N. A.; Pereira, B. M. R.; Celia do Nascimento, M.; Parente, J. P.; Mors, W. B. *Planta Med.* **1994**, *60*, 99−100. (e) Naser-Hijazi, B.; Stolze, B.; Zanker, K. S. *Second proceedings of the International Society of Coumarin Investigators*; Springer: Berlin, 1994. (f) Lewis, R. J.; Singh, O. M.; Simth, C. V.; Skarzynski, T.; Maxwell, A.; Wonacott, A. J.; Wigley, D. B. *EMBO J.* **1996**, *15*, 1412−1420. (g) Levine, C.; Hiasa, H.; Marians, K. J. *Biochim. Biophys. Acta* **1998**, *1400*, 29−43. (h) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97−109. (i) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59−62.

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(5) (a) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamota, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970−3971. (b) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 568−572. (c) Sait, S.; Chounan, Y.; Nogami, T.; Fukushi, T.; Tsuboya, N.; Yamada, Y.; Kitahara, H.; Yamamota, Y. *J. Org. Chem.* **2000**, *65*, 5350−5354. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

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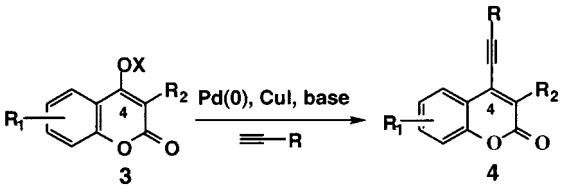
Scheme 1. Syntheses of 4-Alkynylcoumarins



reaction. We then turned our attention to more stable substances, vinyl phosphates, due to their weaker electron-withdrawing properties compared with triflates.

Therefore, 4-hydroxycoumarin was selected as a model and treated with diphenyl or diethyl chlorophophate and Hünig's base in acetonitrile.[8] It gives almost quantitative yields of the corresponding vinyl phosphates **3** [Scheme 1, X = P(O)(OEt)$_2$ or X = P(O)(OPh)$_2$], and both phosphates are stable after heating at 80 °C for 5 h in DMF. However, cross-coupling reactions of these phosphates with phenylacetylene under the Sonogashira conditions gave either a complex mixture (vinyl diphenyl phosphate) or no reaction at all (vinyl diethyl phosphate) after 12 h at 50−60 °C.

In the past decade, much attention has been devoted to utilizing transition metals catalyzed cross-coupling of aryl or vinyl sulfonates with organotin reagents, organoborons, organozincs, and Grignard reagents as well as sulfoximines,[7,9] because those sulfonates are cheaper and more easily accessible from the phenols and enols than their corresponding triflates. As a result, an entirely new class of substrates, other than aryl or vinyl halides (or triflates), could be utilized as starting materials for the transition metal-catalyzed cross-coupling reactions.

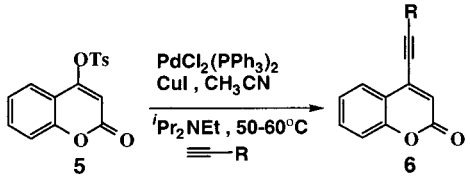
However, there is no report for the palladium-catalyzed cross-couplings of aryl or vinyl sulfonates with terminal acetylenes under Sonogashira reaction conditions. Nevertheless, this reaction is operated by a catalytic amount Cu^I and is relatively insensitive to moisture under mild reaction conditions.

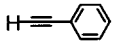
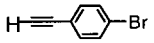
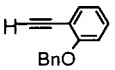
We therefore explored the possibility of using vinyl tosylate **5** (Table 1) as an electrophile for the Sonogashira reaction. Inspired by the recent results of the Stille coupling reaction between tosylate derivatives and organostannanes for carbon−carbon bond formation,[7] we started to investigate the Sonogashira reaction between 4-tosylcoumarin **5** and terminal acetylenes.

The compound **5** (Table 1) was prepared from 4-hydroxycoumarin (commercial available) according to the reported method.[7] Reaction of **5** with a variety of terminal acetylenes in the presence of diisopropylethylamine and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in acetonitrile resulted in the formation of a series of enynes **6** in good to excellent yields as shown in Table 1.

From Table 1 we can find that all the selected terminal acetylenes (except trimethylsilylacetylene) reacted smoothly with tosylate **5** under the Sonogashira conditions between 50 °C and 60 °C in less than 12 h. Due to the low boiling point of trimethylsilylacetylene (bp 53 °C)

Table 1. Palladium-Catalyzed Cross-Couplings of Terminal Acetylenes with 4-Tosylcoumarin 5



Entry	Alkyne[b]	Product	Yield (%)[a]
1		6a	81
2		6b	78
3		6c	72
4	$H{\equiv}(CH_2)_4CH_3$	6d	98
5	$H{\equiv}(CH_2)_7CH_3$	6e	91
6	$H{\equiv}(CH_2)_3Cl$	6f	83
7	$H{\equiv}(CH_2)_3CN$	6g	82
8	$H{\equiv}(CH_2)_3OH$	6h	92
9	$H{\equiv}SiMe_3$	6i	68[c]

[a] Isolated yield bases on 4-tosylcoumarin and refers to a single run. [b] 1.5 equiv of acetylene was used. [c] The reaction was carried out at 25 °C for 48 h.

(entry 9), the coupling reaction of trimethylsilylacetylene with the tosylate **5** was carried out at 25 °C and needed 48 h to complete. Since many functional groups (such as bromo, chloro, hydroxy, and cyano) can tolerate the reaction conditions, the expected enynes **6** were obtained in good to excellent yields (72−92%, entries 1−8).

To secure a combinatorial synthesis of a coumarin library, a further exploration of the generality and scope of this method was carried out by the coupling of diversified tosylates **7** with 1-heptyne, and the results are illustrated in Table 2. The corresponding tosylates were made from the commercially available substituted 4-hydroxycoumarins, and the detailed experimental data are summarized in the Experimental Section.

As illustrated in entries 1−3, substitution groups (such as methyl, methoxy, and chloro) on the coumarin scaffolds do not change the coupling efficiency, and all the reactions went to completion in less than 12 h. The coupling reaction between 3-bromo-4-tosylcoumarin and heptyne (entry 4) gave a double cross-coupling product in a 71% yield.

In addition to the obvious usefulness of the coumarin tosylates for the coupling with terminal acetylenes in the Sonogashira reaction, we wanted to explore the possibility to couple them with organozinc reagents which are commercially available or easily accessible and tolerant to many functional groups (such as ester and lactone).[10]

We therefore carried out a study to evaluate 4-tosylcoumarin **9** coupling with a variety of organozinc reagents (see Table 3).

The reactions proceeded very well when aryl, benzyl, and even 3-cyanopropylzinc bromides (entries 1−3, 5−8)

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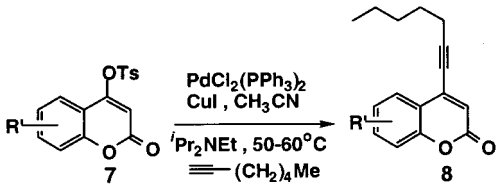
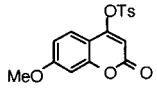
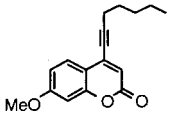
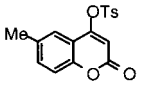
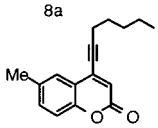
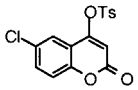
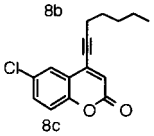
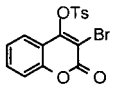
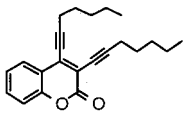
(9) (a) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, *7*, 911. (b) Castulík, J.; Mazal, C. *Tetrahedron Lett.* **2000**, *41*, 2741. (c) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, *4*, 471. (d) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron* **1997**, *53*, 3035. (e) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. (f) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321. (g) Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1990**, *55*, 350.

(10) (a) Erdik, E. *Tetrahedron* **1984**, *40*, 641. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

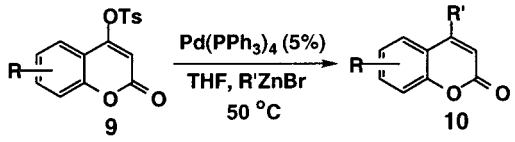
Table 2. Palladium-Catalyzed Cross-Couplings of Various Substituted Tosylates 7 with 1-Heptyne



Entry	Vinyl tosylate	Product	Yield (%)[a]
1		 8a	93
2		 8b	84
3		 8c	84
4		 8d	71

[a] Isolated yield bases on tosylate **7** and 1.5 equiv. of 1-heptyne was used. The yield refers to a single run.

Table 3. the Palladium-catalyzed Cross-couplings of Tosylates 9a and 9b with Organozincs



9a: R = H
9b: R = 6-Me

Entry	Tosylate	Zinc Reagent (R'ZnBr)	Product	Yield (%)[a]
1	9a		10aa	71
2	9a		10ab	85
3	9a	$NC(CH_2)_3ZnBr$	10ac	85
4	9a		10ad	42
5	9a		10ae	91
6	9b		10ba	66
7	9b		10bb	61
8	9b	$NC(CH_2)_3ZnBr$	10bc	82

[a] Isolated yields base on tosylate **9a** and **9b** and refer to a single run. [b] 1.5 equiv of organozinc compound was used.

were employed to react with the tosylates **9a** and **9b**. However, using cyclohexylzinc bromide (entry 4) gave a low yield, presumably due to the β-elimination competing with the reductive elimination, which is in contrast with the result of 3-cyanopropylzinc bromides. We suspected that the remote triple bond of the cyano group in 3-cyanopropylzinc bromide could act as an additional ligand for the palladium intermediates in the cross-coupling reaction.[11] Therefore, the reductive elimination is more favorable than the β-elimination; as a result, a better yield is obtained (entry 8).

In summary, the cross-coupling reactions between 4-tosylcoumarins and terminal acetylenes and organozinc reagents have been investigated. The chemistry described above illustrates the usefulness of 4-tosyl-coumarins as an alternative for the palladium-catalyzed cross-coupling reactions. The mild reaction conditions and superiority of those tosylates over their corresponding vinyl triflates (in terms of their stability, cost, and availability of reagents for their syntheses) should make them the ideal substrates for a combinatorial synthesis of coumarin library on solid supports. The application of these tosylates to synthesize a coumarin library on silyl linker-based polystyrene macrobeads is currently under investigation in our laboratory.

Experimental Section

General Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under argon atmosphere. Reaction solvents were commercially purchased from Aldrich without further purification, and reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light, *p*-anisaldehyde stain, or phosphomolybdic acid stain. Flash chromatography was performed on Merck Silica Gel 60 (230−400 mesh) using reagent grade hexanes, dichloromethane, and ACS grade ethyl acetate, methanol, and diethyl ether. MS spectra were obtained on a Micromass Platform LCZ with Alliance 2690. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA 500M Hz spectrometer and are referenced to residual solvent peaks ($CDCl_3$: ^{1}H NMR at δ 7.24 and ^{13}C NMR at δ 77.0). ^{1}H−^{1}H couplings are assumed to be first order, and corresponding peaks are reported as s (singlet), d (doublet), t (triplet), q (quarter), and m (multiplet) as well as b (broad).

General Procedure for Synthesis of 4-Alkynylcoumarins: A round-bottom flask (25 mL) was flame-dried under high vacuum. Upon cooling, 4-tosylcoumarin (0.5 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 10 mol %), CuI (9.6 mg, 10 mol %), acetonitrile (5 mL), *N*,*N*-(diisopropylethyl)amine (0.13 mL, 1.5 equiv) and acetylene (1.5 equiv) were added. The reaction mixture was stirred overnight between 50 and 60 °C. Following completion of the reaction that was monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (20 mL), and filtered through a short silica gel bed. The filtrate was concentrated to a residue that was purified by flash chromatography to give the corresponding product.

4-(2-Phenylethynyl)coumarin (6a): 81% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.43−7.52 (m, 3H), 7.59 (t, J = 8.5, 7.0 Hz, 1H), 7.66 (d, J = 7.5 Hz, 2H), 7.97 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.5, 153.8, 146.7, 137.5, 132.5, 132.4, 130.5, 129.0, 126.9, 124.7, 121.4, 118.6, 117.3, 102.4, 83.4. MS (APCI) [$C_{17}H_{10}O_2$], m/z ($M^+ + 1$): calcd 247, found 247.

4-(2-(4-Bromophenyl)ethynyl)coumarin (6b): 78% yield as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 7.37−7.41 (m, 2H), 7.52−7.64 (m, 5H), 7.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz); δ 160.3, 153.8, 137.1, 133.8, 133.3, 132.6, 132.3, 132.0, 126.8, 125.1, 124.8, 120.3, 118.9, 118.4, 117.3, 101.0, 84.0. MS (APCI) [$C_{17}H_9BrO_2$], m/z ($M^+ + 1$): calcd 325, found 325.

4-(2-(2-Phenylmethoxy)phenylethynyl)coumarin (6c): 72% yield as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22

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(s, 2H), 6.60 (s, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.03−7.08 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.41−7.56 (m, 7H), 7.62 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.7, 160.5, 153.7, 137.9, 136.5, 134.4, 132.2, 132.1, 129.0, 128.6, 128.1, 127.4, 124.6, 121.3, 118.7, 117.7, 117.0, 112.4, 111.3, 99.6, 87.6, 71.0. MS (APCI) [$C_{24}H_{16}O_3$], m/z ($M^+ + 1$): calcd 353, found 353.

4-(1-Heptynyl)coumarin (6d): 98% yield as a brownish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.0 Hz, 3H), 1.38−1.46 (m, 2H), 1.46−1.54 (m, 2H), 1.68−1.76 (m, 2H), 2.58 (t, J = 7.5, 7.0 Hz, 2H), 6.51 (s, 1H), 7.28−7.34 (m, 2H), 7.52−7.60 (m, 1H), 7.86 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 161.0, 154.0, 138.2, 132.6, 127.0, 124.8, 119.0, 118.4, 117.2, 105.1, 75.6, 31.4, 28.1, 22.8, 20.2, 14.3. MS (APCI) [$C_{16}H_{16}O_2$], m/z ($M^+ + 1$): calcd 241, found 241.

4-(1-Decynyl)coumarin (6e): 91% yield as a brownish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0, 5.5 Hz, 3H), 1.24−1.42 (m, 8H), 1.46−1.54 (m, 2H), 1.68−1.76 (m, 2H), 2.58 (t, J = 7.0 Hz, 2H), 6.51 (s, 1H), 7.32 (t, J = 8.0, 7.0 Hz, 2H), 7.56 (t, J = 8.0, 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.7, 153.8, 138.3, 132.3, 127.0, 124.5, 119.1, 118.5, 117.1, 105.4, 75.1, 32.0, 29.4, 29.3, 29.2, 28.5, 22.9, 20.1, 14.3. MS (APCI) [$C_{19}H_{22}O_2$], m/z ($M^+ + 1$): calcd 283, found 283.

4-(5-Chloro-1-pentynyl)coumarin (6f): 83% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15−2.20 (m, 2H), 2.81 (t, J = 7.0, 6.5 Hz, 2H), 3.75 (t, J = 6.5, 6.0 Hz, 2H), 6.53 (s, 1H), 7.32−7.35 (m, 2H), 7.56−7.58 (m, 1H), 7.84 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.2, 153.5, 137.6, 132.2, 126.6, 124.4, 118.7, 118.6, 117.0, 102.4, 75.6, 43.4, 30.8, 17.3. MS (APCI) [$C_{14}H_{11}ClO_2$], m/z ($M^+ + 1$): calcd 247, found 247.

4-(5-Cyano-1-pentynyl)coumarin (6g): 82% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04−2.12 (m, 2H), 2.60 (dd, J = 7.0, 2.5 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 6.49 (s, 1H), 7.28−7.33 (m, 2H), 7.50−7.60 (m, 1H), 7.70−7.80 (m, 1H); ^{13}C NMR (125.7 MHz) δ 160.3, 153.7, 137.5, 132.6, 126.8, 124.7, 119.1, 118.9, 118.6, 117.2, 101.3, 76.4, 24.4, 19.1, 16.7. MS (APCI): [$C_{15}H_{11}NO_2$], m/z ($M^+ + 1$): calcd 238, found 238.

4-(5-Hydroxy-1-pentynyl)coumarin (6h): 92% yield as a yellowish oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90−2.00 (m, 2H), 2.00−2.40 (br, 1H), 2.70 (t, J = 7.5, 7.0 Hz, 2H), 3.84 (t, J = 6.5, 5.5 Hz, 2H), 6.45 (s, 1H), 7.25−7.30 (m, 2H), 7.50−7.52 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.8, 153.7, 138.3, 132.4, 126.9, 124.7, 118.9, 118.4, 117.1, 104.7, 75.2, 61.4, 31.2, 16.6. MS (APCI) [$C_{14}H_{12}O_3$], m/z ($M^+ + 1$): calcd 229, found 229.

4-(2-Trimethylsilylethynyl)coumarin (6i): 68% yield as a colorless oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 0.35 (s, 9H), 6.57 (s, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.4, 153.8, 137.2, 132.5, 126.9, 124.7, 119.4, 118.5, 117.2, 109.8, 97.7, −0.2. MS (APCI) [$C_{14}H_{14}O_2Si$], m/z ($M^+ + 1$): calcd 243, found 243.

7-Methoxy-4-(1-heptynyl)coumarin (8a): 93% yield as a yellowish oil;^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, J = 7.0 Hz, 3H), 1.2−1.7 (m, 6H), 2.59 (t, J = 7.0 Hz, 2H), 3.85 (s, 3 H), 6.34 (s, 1H), 6.9 (m, 2H), 7.6 (d, J = 9.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 163.6, 160.3, 155.5, 137.7, 127.9, 115.1, 113.3, 112.4, 105.7, 101.6, 75.4, 56.7, 31.3, 28.0, 22.3, 19.7, 14.5. MS (APCI) [$C_{17}H_{18}O_3$], m/z ($M^+ + 1$): calcd 271, found 271.

6-Methyl-4-(1-heptynyl)coumarin (8b): 84% yield as a yellowish oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (dt, J = 6.5, 3.0 Hz, 3H), 1.36−1.46 (m, 2H), 1.46−1.56 (m, 2H), 1.68−1.76 (m, 2H), 2.44 (s, 3H), 2.58 (dt, J = 7.5, 3.0 Hz, 2H), 6.48 (s, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H); ^{13}C NMR (125.7 MHz) δ 160.9, 151.9, 138.3, 134.3, 133.3, 126.7, 118.7, 118.4, 116.9, 105.1, 75.2, 31.4, 28.1, 22.4, 21.1, 20.1, 14.2. MS (APCI) [$C_{17}H_{18}O_2$], m/z ($M^+ + 1$): calcd 255, found 255.

6-Chloro-4-(1-heptynyl)coumarin (8c): 84% yield as a yellowish oil.^{1}H NMR (500 MHz, DMSO-d_6) δ 0.9 (m, 3H), 1.2−1.8 (m, 6H), 2.59 (t, J = 7.0 Hz, 2H), 6.53 (s, 1H), 7.28 (m, 1H), 7.50 (m, 1H), 7.81 (s, 1H). ^{13}C NMR (125.7 MHz) δ (ppm) 160.0, 152.2, 137.3, 1322, 130.0, 126.4, 120.2, 119.3, 118.6, 106.3, 74.6, 31.4, 28.1, 22.4, 20.1, 14.2. MS (APCI) [$C_{16}H_{15}ClO_2$], m/z ($M^+ + 1$): calcd 275, found 275.

3, 4-Di(1-heptynyl)coumarin (8d): 71% yield as a yellowish oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.9 (m, 6H), 1.2−1.8 (m, 12H), 2.52 (m, 2H), 2.69 (m, 2H), 7.40 (m, 1H), 7.50 (m, 2H), 7.62 (m, 1H), 7.79 (m, 1H); ^{13}C NMR (125.7 MHz) δ 159.0, 152.4, 137.8, 133.1, 127.1, 125.6, 118.9, 117.2, 114.8, 110.6, 102.4, 76.4, 75.7, 31.2, 31.1, 28.3, 28.1, 22.4, 22.3, 20.1, 19.9, 14.5. MS (APCI) [$C_{23}H_{26}O_2$], m/z ($M^+ + 1$): calcd 335, found 335.

General Procedure for the Palladium-Catalyzed Reactions of 4-Tosylatecoumarin with Zinc Reagents. A round-bottom flask (25 mL) was flame-dried under high vacuum. Upon cooling, 4-tosylylcoumarin (0.5 mmol), tetrakis(triphenylphosphine)palladium(0) (28.8 mg, 5 mol %), tetrahydrofuran (5 mL), and zinc reagent (0.75 mmol) were added. The reaction mixture was stirred overnight at 50 °C. Following completion of the reaction as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (20 mL), and filtered through a short silica gel bed. The filtrate was concentrated to a residue that was purified by flash chromatography to give the corresponding product.

4-Phenylcoumarin (10aa):[7] 71% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (s, 1H), 7.20−7.30 (m, 2H), 7.40−7.60 (m, 7H); ^{13}C NMR (125.7 MHz) δ 161.0, 155.9, 154.5, 135.5, 132.2, 129.9, 129.1, 128.7, 127.3, 124.4, 119.3, 117.6, 115.5. MS (APCI) [$C_{15}H_{10}O_2$], m/z ($M^+ + 1$): calcd 223, found 223.

4-(Phenylmethyl)coumarin (10ab): 85% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (s, 2H), 6.16 (s, 1H), 7.25−7.38 (m, 7H), 7.50−7.58 (m, 1H), 7.68 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 161.1, 154.8, 154.0, 136.2, 132.0, 129.3, 129.2, 127.5, 124.9, 124.5, 119.5, 117.5, 116.0, 38.3. MS (APCI) [$C_{16}H_{12}O_2$], m/z ($M^+ + 1$): calcd 237, found 237.

4-(3-Cyanopropyl)coumarin (10ac): 85% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05−2.18 (m, 2H), 2.55 (t, J = 7.0, 6.5 Hz, 2H), 2.99 (t, J = 8.0, 7.5 Hz, 2H), 6.33 (s, 1H), 7.33−7.39 (m, 2H), 7.58 (t, J = 8.5, 7.5 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.7, 154.1, 153.8, 132.4, 124.8, 124.2, 118.9, 118.8, 117.8, 114.8, 30.5, 24.1, 17.2. MS (APCI) [$C_{13}H_{11}NO_2$], m/z ($M^+ + 1$): calcd 214, found 214.

4-Cyclohexylcoumarin (10ad): 42% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32−1.52 (m, 5H), 1.85−2.02 (m, 5H), 2.90−2.95 (m, 1H), 6.32 (s, 1H), 7.31−7.38 (m, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 161.8, 161.0, 154.1, 131.6, 124.3, 124.2, 119.0, 117.8, 111.9, 39.2, 32.7, 26.8, 26.3. MS (APCI) [$C_{15}H_{16}O_2$], m/z ($M^+ + 1$): calcd 229, found 229.

2-Coumarinthiophene (10ae):[7] 91% yield as a yellowish oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 7.25−7.34 (m, 2H), 7.42−7.45 (m, 2H), 7.58−7.61 (m, 2H), 7.94 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ 160.7, 154.4, 148.2, 136.2, 132.4, 129.6, 128.8, 128.4, 126.9, 124.6, 118.6, 117.7, 115.4. MS (APCI) [$C_{13}H_8O_2S$], m/z ($M^+ + 1$): calcd 229, found 229.

6-Methyl-4-phenylcoumarin (10ba): 66% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 6.37 (s, 1H), 7.25−7.58 (m, 8H); ^{13}C NMR (125.7 MHz) δ 161.2, 155.9, 152.6, 135.6, 134.1, 133.2, 129.8, 129.1, 128.8, 126.9, 118.9, 117.3, 115.4, 21.2. MS (APCI) [$C_{16}H_{12}O_2$], m/z ($M^+ + 1$): calcd 237, found 237.

6-Methyl-4-(phenylmethyl)coumarin (10bb): 61% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.10 (s, 2H), 6.07 (s, 1H), 7.20−7.46 (m, 8H); ^{13}C NMR (125.7 MHz) δ 161.4, 154.8, 152.1, 136.2, 134.1, 132.9, 129.4, 129.2, 127.5, 124.6, 119.2, 117.2, 115.8, 38.2, 21.3. MS (APCI) [$C_{17}H_{14}O_2$], m/z ($M^+ + 1$): calcd 251, found 251.

6-Methyl-4-(3-cyanopropyl)coumarin (10bc): 82% yield as a colorless oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08−2.14 (m, 2H), 2.45 (s, 3H), 2.54 (t, J = 7.0, 6.5 Hz, 2H), 2.97 (dd, J = 8.0, 7.5 Hz, 2H), 6.30 (s, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.28−7.41 (m, 2H); ^{13}C NMR (125.7 MHz) δ 160.9, 153.6, 152.2, 134.5, 133.4, 124.0, 118.9, 118.6, 117.5, 114.7, 30.4, 24.0, 21.3, 17.2. MS (APCI) [$C_{14}H_{13}NO_2$], m/z ($M^+ + 1$): calcd 228, found 228.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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