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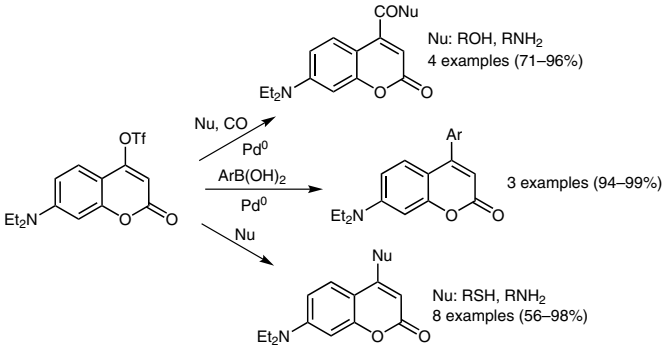
# Coumaryl Triflate, a Versatile Building Block for the Modification of Coumarins and for Fluorescence Labeling

**Uli Kazmaier**[*a]
**Tamara Doroshenko**[a]
**Kevin Bauer**[a]
**Isabel Filbrich**[a]
**Andreas Grueter**[b]
**Gregor Jung**[b]
**Angelika Ullrich**[a]

[a] Universität des Saarlandes, Organische Chemie, 66123 Saarbrücken, Germany
u.kazmaier@mx.uni-saarland.de
[b] Universität des Saarlandes, Biophysikalische Chemie, 66123 Saarbrücken, Germany

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**Abstract** Coumaryl triflate can be used for a wide range of substitution reactions, either under Pd-catalyzed conditions or via direct nucleophilic substitutions, and is therefore an ideal substrate for the fluorescence labeling of functionalized compounds, such as amino acids.

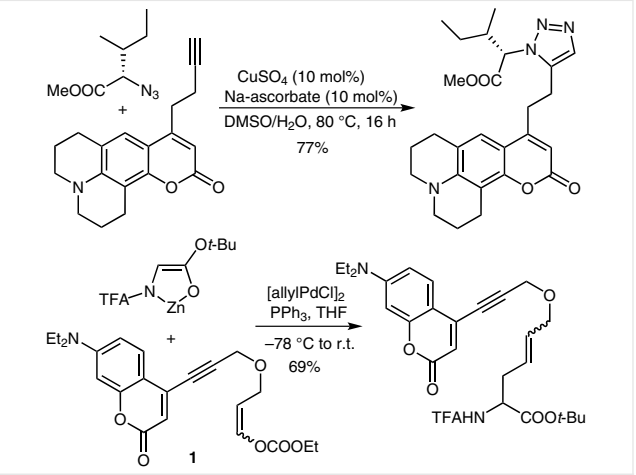
**Key words** amino acids, carbonylation, coumarins, fluorescence labeling, palladium, substitution

In the life sciences, fluorescence labeling plays an important role for the investigation of cellular processes and the three-dimensional imaging of tissues and living cells.[1] For the labeling of proteins, for example, a wide range of fluorescence dyes can be used.[2] Besides BODIPYs[3] and fluorescein derivatives,[4] coumarins also play an important role, especially those with electron-donating groups at the 7-position.[5] In general, these coumarins show an excellent fluorescence quantum yield, making them extremely suitable for fluorescence microscopy and the development of fluorescence labels.[6] Recently, we could show that 7-dialkylamino-substituted fluorescence labels can be introduced into functionalized amino acids and peptides[7] via the popular azide-alkyne click chemistry,[8] or as backbone modification via Pd-catalyzed allylic alkylation[9] using coumaryl-substituted allylic carbonates such as **1** (Scheme 1).[10]

A key building block in the synthesis of **1** and related structures was coumaryl triflate **2** (Figure 1), which could be converted into **1** via Sonogashira coupling. With this interesting building block **2** in hand, we were interested to study its properties and examine its uses for other reactions.

Triflate **2** can easily be obtained in two steps from *m*-*N*,*N*-diethylaminophenol.[10,11] Comparable to the previously described Sonogashira coupling[10] also Suzuki coupling proceeded nicely and in almost quantitative yields (Scheme 2). These aryl-substituted derivatives are interesting building blocks used, for example, in fluorescent neurosensors.[12]

Enlarging the π-system by introduction of an additional phenyl ring resulted in a bathochromic shift of the absorption maximum ($\lambda_{abs}$) from 351 nm (**2**) to ~375 nm (**3**), while the emission maximum ($\lambda_{em}$) shifted from 384 nm (**2**) to 454–464 nm (**3**).




**Scheme 1** Fluorescence labeling of amino acids via click reaction and Pd-catalyzed allylic alkylation

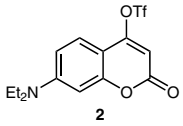
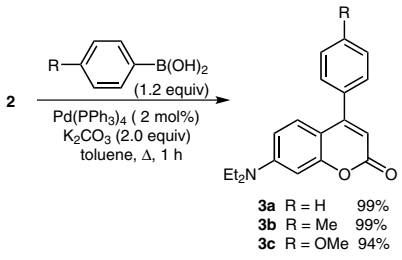
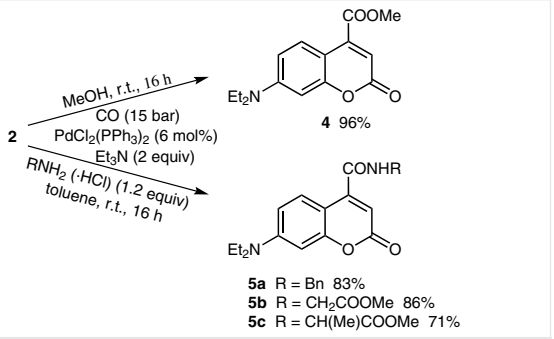



**Figure 1** Coumaryl triflate **2**




**Scheme 2** Suzuki couplings of coumaryl triflate **2**

With these good results in hand, carbonylation reactions[13] of **2** were next investigated. Our initial experiment was carried out in absolute methanol at room temperature. However, at a CO pressure of 1 atm, only 13% of the desired methyl ester **4** was obtained, while most of the triflate **2** could be recovered. Significantly better yields could be obtained if the pressure was increased to 15 bar (Scheme 3). Under these conditions ester **4** could be obtained in excellent yield.

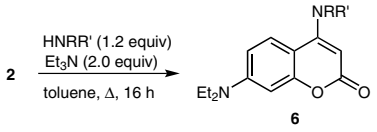



**Scheme 3** Carbonylative couplings of coumaryl triflate **2**

The reaction probably proceeds via an acyl–Pd intermediate,[13] which is attacked by the nucleophilic solvent. Therefore, one might expect also good results with other good nucleophiles, for example, amines. And indeed, good yields of **5** were obtained with primary amines, including amino acid esters (Scheme 3). These could be used as salts if an excess of base was added. Therefore, triflate **2** is also suitable for amino acid fluorescence labeling. Incorporation of CO resulted also in a dramatic bathochromic shift of the absorption and emission maxima (compared to **2**) by 33–35 nm ($\lambda_{abs}$) and 133–141 nm ($\lambda_{em}$), respectively.

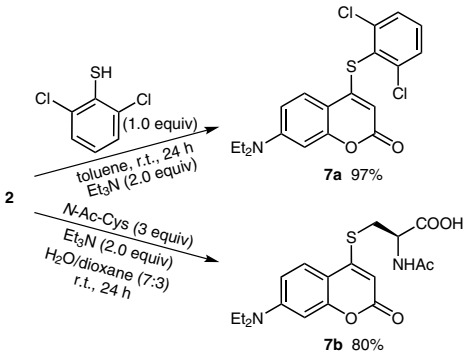
Interestingly, a different reaction behavior was observed with more nucleophilic secondary amines such as morpholine. In this case, no CO insertion was observed and the amine directly replaced the triflate. Therefore, also no Pd catalyst is required in this reaction, and best results were obtained by refluxing the reaction mixture in toluene overnight (Table 1). While cyclic secondary amines gave almost a quantitative yield of **6** (Table 1, entries 1, 2), the results were little worse with the more flexible secondary amines (entries 3–5). But even ephedrine could be fluorescence-labeled in acceptable yield (entry 5). This is also true for Leu-OMe as a representative of the amino acid derivatives (entry 6). Fluorescence is maintained in all 4-amino-substituted derivatives with little spectral shifts compared to **2**.

**Table 1** Direct Aminations of Coumaryl Triflate **2**




| Entry | HNRR′ | Product | Yield (%) |
|---|---|---|---|
| 1 | morpholine | **6a** | 95 |
| 2 | piperidine | **6b** | 98 |
| 3 | diethylamine | **6c** | 68 |
| 4 | dibenzylamine | **6d** | 60 |
| 5 | ephedrine | **6e** | 56 |
| 6 | Leu-OMe | **6f** | 62 |

One of the highly nucleophilic functionalities found in nature is the SH group of cysteine, which should also be a good candidate for fluorescence labeling with **2**. Therefore, we also investigated substitutions with aromatic and aliphatic thiols. The reaction of 2,6-dichlorothiophenol under the previous reaction conditions provided the expected product **7a** in almost quantitative yield, even at room temperature (Scheme 4). To prove whether triflate **2** might also survive aqueous conditions, generally used for peptide and protein labeling, the labeling of *N*-protected cysteine was investigated in an aqueous 1,4-dioxane solution. Also under these conditions, the reaction proceeded nicely at room temperature, and the somewhat lower yield of **7b** can be explained by a competitive oxidation of the cysteine to cystine under the reaction conditions.




**Scheme 4** Fluorescence labeling of thiols using coumaryl triflate **2**

In conclusion, we have shown that coumaryl triflate **2** can be subjected to a wide range of modifications, either under Pd-catalyzed conditions or via direct nucleophilic

substitutions. Thiols are found to be significantly more reactive than amines, and chemoselective peptide labelings are currently under investigation.

All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of $N_2$ or argon. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm). Mixtures of $CH_2Cl_2$ and EtOAc were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, $KMnO_4$ solution, or ninhydrin solution. Melting points were determined with a Dr. Tottoli (Büchi) melting point apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AVII-400 [400 MHz ($^1H$) and 100 MHz ($^{13}C$)] spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS; $CHCl_3$ was used as the internal standard. Mass spectra were recorded with a Finnigan MAT 95Q spectrometer using the CI technique. A Jasco V-650 spectrophotometer was used to measure the absorption spectra, while a Jasco FP-6500 was used for the fluorescence spectra. Quantum yields of selected compounds (5 µM in DMSO) were determined on a Quantaurus-QY Absolute PL Quantum Yield Spectrometer C 11347 (Hamamatsu). Elemental analyses were performed at Saarland University.

### Suzuki Coupling of Coumaryl Triflate 2; General Procedure

To a solution of $Pd(PPh_3)_4$ (2 mol%), $K_2CO_3$ (2 equiv), and triflate **2**[10] (1 equiv) in toluene (5 mL/mmol) was added arylboronic acid (1.2 equiv) under $N_2$ atmosphere at r.t. and the reaction mixture was refluxed until complete conversion of the coumarin was observed (TLC). Afterwards, the reaction was quenched with aq 1 M $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried (anhyd $Na_2SO_4$), concentrated, and the crude product was purified by flash chromatography (silica gel).

### 7-(*N*,*N*-Diethylamino)-4-phenyl-2*H*-chromen-2-one (3a)[14]

According to the general procedure for Suzuki coupling, phenylboronic acid (29 mg, 0.24 mmol) was added to a solution of triflate **2** (73 mg, 0.20 mmol), $Pd(PPh_3)_4$ (4.6 mg, 4 µmol, 2 mol%), and $K_2CO_3$ (33 mg, 0.24 mmol) in anhyd toluene (1 mL). The reaction mixture was refluxed for 1 h. After workup and column chromatography (silica gel, PE–EtOAc 7:3), **3a** was isolated as a yellow solid; yield: 59 mg (0.20 mmol, 99%); mp 119–120 °C; $R_f$ = 0.25 (PE–EtOAc 7:3).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 6.01 (s, 1 H), 6.51 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.57 (d, *J* = 2.4 Hz, 1 H), 7.25 (d, *J* = 9.1 Hz, 1 H), 7.40–7.49 (m, 5 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 12.5, 44.8, 97.9, 108.0, 108.3, 108.5, 127.9, 128.4, 128.6, 129.2, 136.3, 150.6, 156.2, 156.8, 162.2.

HRMS (CI): *m*/*z* calcd for $C_{19}H_{19}NO_2$ $(M)^+$: 293.1410; found: 293.1410.

UV (DMSO): $\lambda_{max}$ (abs) = 376 nm; $\lambda_{max}$ (em) = 464 nm.

Anal. Calcd for $C_{19}H_{19}NO_2$ (293.37): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.76; H, 6.71; N, 4.62.

### 7-(*N*,*N*-Diethylamino)-4-(*p*-tolyl)-2*H*-chromen-2-one (3b)

According to the general procedure for Suzuki coupling, *p*-tolylboronic acid (33 mg, 0.24 mmol) was added to a solution of triflate **2** (73 mg, 0.20 mmol), $Pd(PPh_3)_4$ (4.6 mg, 4 µmol, 2 mol%), and $K_2CO_3$ (33 mg, 0.24 mmol) in anhyd toluene (1 mL). The reaction mixture was refluxed for 1 h. After workup and column chromatography (silica gel, PE–EtOAc 7:3), **3b** was isolated as a yellow solid; yield: 61 mg (0.20 mmol, 99%); mp 121–123 °C; $R_f$ = 0.22 ($CH_2Cl_2$–EtOAc 98:2).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 6 H), 2.46 (s, 3 H), 3.43 (q, *J* = 7.1 Hz, 4 H), 6.02 (s, 1 H), 6.53 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 7.28–7.38 (m, 5 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 12.5, 21.4, 44.8, 97.9, 108.0, 108.2, 108.4, 128.0, 128.4, 129.3, 133.4, 139.4, 150.6, 156.2, 156.8, 162.3.

HRMS (CI): *m*/*z* calcd for $C_{20}H_{21}NO_2$ $(M)^+$: 307.1567; found: 307.1578.

UV (DMSO): $\lambda_{max}$ (abs) = 373 nm; $\lambda_{max}$ (em) = 454 nm.

Anal. Calcd for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 77.82; H, 6.94; N, 4.50.

### 7-(*N*,*N*-Diethylamino)-4-(4-methoxyphenyl)-2*H*-chromen-2-one (3c)[12]

According to the general procedure for Suzuki coupling, 4-methoxyphenylboronic acid (36 mg, 0.24 mmol) was added to a solution of triflate **2** (73 mg, 0.20 mmol), $Pd(PPh_3)_4$ (4.6 mg, 4 µmol, 2 mol%), and $K_2CO_3$ (33 mg, 0.24 mmol) in anhyd toluene (1 mL). The reaction mixture was refluxed for 1 h. After workup and column chromatography (silica gel, hexanes–EtOAc 7:3), **3c** was isolated as a yellow solid; yield: 61 mg (0.19 mmol, 94%); mp 121–123 °C; $R_f$ = 0.59 ($CH_2Cl_2$–EtOAc 95:5).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 3.88 (s, 3 H), 5.99 (s, 1 H), 6.52 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.56 (d, *J* = 2.6 Hz, 1 H), 7.01 (dt, *J* = 8.8, 2.8 Hz, 2 H), 7.31 (d, *J* = 9.1 Hz, 1 H), 7.39 (dt, *J* = 8.8, 2.8 Hz, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 12.4, 44.7, 55.4, 97.9, 107.9, 108.0, 108.4, 114.1, 127.9, 128.5, 129.8, 150.5, 155.8, 156.8, 160.5, 162.3.

HRMS (CI): *m*/*z* calcd for $C_{20}H_{21}NO$ $(M)^+$: 323.1516; found: 323.1488.

UV (DMSO): $\lambda_{max}$ (abs) = 390 nm; $\lambda_{max}$ (em) = 482 nm; $\Phi_F$ = 0.71.

### Methyl 7-(*N*,*N*-Diethylamino)-2-oxo-2*H*-chromene-4-carboxylate (4)

$Pd(PPh_3)_2Cl_2$ (8.4 mg, 12 µmol, 10 mol%) and $Et_3N$ (33 µL, 24.3 mg, 0.24 mmol) were added to a solution of triflate **2** (44 mg, 0.12 mmol) in anhyd toluene (1.6 mL) containing MeOH (0.2 mL). The reaction mixture was stirred under CO atmosphere (15 bar) in an autoclave at r.t. overnight. Afterwards, the reaction was quenched with aq 1 N $KHSO_4$, and extracted with EtOAc (3 ×). The combined organic layers were filtered through Celite and dried (anhyd $Na_2SO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$) to furnish **4** as a yellow solid; yield: 32 mg (0.115 mmol, 96%); mp 119–120 °C; $R_f$ = 0.33 (PE–EtOAc 7:3).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H), 3.42 (q, *J* = 7.1 Hz, 4 H), 3.96 (s, 3 H), 6.51 (d, *J* = 2.6 Hz, 1 H), 6.52 (s, 1 H), 6.60 (dd, *J* = 9.2, 2.6 Hz, 1 H), 8.00 (d, *J* = 9.2 Hz, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 12.6, 44.8, 52.8, 97.7, 105.0, 109.1, 111.4, 127.7, 150.8, 157.1, 160.8, 165.1. Signal for the $CO_2Me$ group was not observed.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{17}NO_4$ $(M)^+$: 275.1158; found: 275.1171.

UV (DMSO): $\lambda_{max}$ (abs) = 396 nm; $\lambda_{max}$ (em) = 536 nm.

Anal. Calcd for $C_{15}H_{17}NO_4$ (275.30): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.49; H, 6.11; N, 4.92.

### Palladium-Catalyzed Aminocarbonylations of Coumaryl Triflate 2; General Procedure

$Pd(PPh_3)_2Cl_2$ (10 mol%) and $Et_3N$ (2 equiv) were added to a solution of triflate **2** (1 equiv) and the corresponding amine (1.2 equiv) in anhyd toluene (10 mL/mmol). The reaction mixture was stirred under CO atmosphere (15 bar) overnight before it was diluted with $CH_2Cl_2$ and quenched with aq 1 M $NH_4Cl$. The aqueous layer was extracted with $CH_2Cl_2$ (3 ×) and the combined organic layers were dried (anhyd $Na_2SO_4$). The solvent was evaporated in vacuo and the crude product was purified by column chromatography.

### *N*-Benzyl-7-(*N*,*N*-diethylamino)-2-oxo-2*H*-chromene-4-carboxamide (5a)

According to the general procedure for Pd-catalyzed aminocarbonylations, $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol, 10 mol%) and $Et_3N$ (55 µL, 40 mg, 0.40 mmol) were added to a solution of triflate **2** (73 mg, 0.20 mmol) and benzylamine (26 µL, 25.7 mg, 0.24 mmol) in anhyd toluene (2 mL). The reaction mixture was stirred under CO atmosphere (15 bar) at r.t. overnight. After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 100:0, 95:5), **5a** was isolated as a yellow solid; yield: 67 mg (0.17 mmol, 83%); mp 169–170 °C; $R_f$ = 0.45 ($CH_2Cl_2$–EtOAc 95:5).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 6 H), 3.39 (q, *J* = 7.1 Hz, 4 H), 4.61 (d, *J* = 5.9 Hz, 2 H), 6.03 (s, 1 H), 6.41 (d, *J* = 2.5 Hz, 1 H), 6.54 (dd, *J* = 9.1, 2.5 Hz, 1 H), 6.83 (t, *J* = 5.4 Hz, 1 H), 7.26–7.37 (m, 5 H), 7.59 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.5, 43.8, 44.8, 97.6, 105.1, 106.4, 109.2, 127.5, 127.8, 127.8, 128.9, 137.5, 149.4, 151.1, 157.0, 161.9, 165.3.

HRMS (CI): *m*/*z* calcd for $C_{21}H_{22}N_2O_3$ $(M)^+$: 350.1625; found: 350.1631.

UV (DMSO): $\lambda_{max}$ (abs) = 395 nm; $\lambda_{max}$ (em) = 542 nm; $\Phi_F$ = 0.47.

Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found: C, 72.01; H, 6.41; N, 7.89.

### [7-(*N*,*N*-Diethylamino)-2-oxo-2*H*-chromene-4-carbonyl]glycine Methyl Ester (5b)

According to the general procedure for Pd-catalyzed aminocarbonylations, $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol, 10 mol%) and $Et_3N$ (55 µL, 40 mg, 0.40 mmol) were added to a solution of triflate **2** (73 mg, 0.20 mmol) and glycine methyl ester hydrochloride (30 mg, 0.24 mmol) in anhyd toluene (2 mL). The reaction mixture was stirred under CO atmosphere (15 bar) at r.t. overnight. After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 95:5 then 90:10), **5b** was isolated as a yellow solid; yield: 57 mg (0.17 mmol, 86%); mp 141–142 °C; $R_f$ = 0.19 ($CH_2Cl_2$–EtOAc 8:2).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 3.81 (s, 3 H), 4.24 (d, *J* = 5.5 Hz, 2 H), 6.13 (s, 1 H), 6.47 (d, *J* = 2.3 Hz, 1 H), 6.58 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.69 (br s, 1 H), 7.64 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 41.4, 44.8, 52.7, 97.7, 104.9, 106.7, 109.2, 127.5, 148.7, 151.2, 157.1, 161.7, 165.6, 169.7.

HRMS (CI): *m*/*z* calcd for $C_{17}H_{20}N_2O_5$ $(M)^+$: 332.1367; found: 332.1361.

UV (DMSO): $\lambda_{max}$ (abs) = 386 nm; $\lambda_{max}$ (em) = 525 nm.

### [7-(*N*,*N*-Diethylamino)-2-oxo-2*H*-chromene-4-carbonyl]-(*S*)-alanine Methyl Ester (5c)

According to the general procedure for Pd-catalyzed aminocarbonylations, $Pd(PPh_3)_2Cl_2$ (14 mg, 20 µmol, 10 mol%) and $Et_3N$ (55 µL, 40 mg, 0.40 mmol) were added to a solution of triflate **2** (73 mg, 0.20 mmol) and (*S*)-alanine methyl ester hydrochloride (33 mg, 0.24 mmol) in anhyd toluene (2 mL). The reaction mixture was stirred under CO atmosphere (15 bar) at r.t. overnight. After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 95:5), **5c** was isolated as a yellow solid; yield: 49 mg (0.14 mmol, 71%); mp 144–146 °C; $R_f$ = 0.19 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 6 H), 1.53 (d, *J* = 7.2 Hz, 3 H), 3.38 (q, *J* = 7.1 Hz, 4 H), 3.78 (s, 3 H), 4.74 (qd, *J* = 7.2, 7.2 Hz, 1 H), 6.09 (s, 1 H), 6.43 (d, *J* = 2.3 Hz, 1 H), 6.55 (dd, *J* = 9.1, 2.4 Hz, 1 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 7.59 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 18.0, 44.8, 48.5, 52.7, 97.6, 105.0, 106.6, 109.2, 127.5, 149.0, 151.1, 157.0, 161.8, 165.1, 172.8.

HRMS (CI): *m*/*z* calcd for $C_{18}H_{22}N_2O_5$ $(M)^+$: 346.1523; found: 346.1525.

UV (DMSO): $\lambda_{max}$ (abs) = 386 nm; $\lambda_{max}$ (em) = 520 nm.

### Aminations of Coumaryl Triflate 2; General Procedure

$Et_3N$ (2 equiv) was added to a solution of triflate **2** (1 equiv) and the corresponding amine (1.2–1.5 equiv) in anhyd toluene (10 mL/mmol). The reaction mixture was refluxed overnight. After cooling to r.t., the mixture was diluted with $CH_2Cl_2$ and quenched with aq 1 M $NH_4Cl$. The aqueous layer was extracted with $CH_2Cl_2$ (3 ×) and the combined organic layers were dried (anhyd $Na_2SO_4$). The solvent was evaporated in vacuo and the crude product was purified by column chromatography.

### 7-(*N*,*N*-Diethylamino)-4-morpholino-2*H*-chromen-2-one (6a)

According to the general procedure for aminations, triflate **2** (44 mg, 0.12 mmol) was reacted with morpholine (12 µL, 15.8 mg, 0.18 mmol) and $Et_3N$ (33 µL, 24 mg, 0.24 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 95:5), **6a** was isolated as a yellow solid; yield: 34 mg (0.11 mmol, 95%); mp 132–133 °C; $R_f$ = 0.32 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H), 3.22 (m, 4 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 3.89 (m, 4 H), 5.45 (s, 1 H), 6.48 (d, *J* = 2.6 Hz, 1 H), 6.54 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.36 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.5, 44.7, 51.5, 66.5, 92.9, 98.1, 104.3, 107.9, 125.6, 150.3, 156.7, 162.0, 163.6.

HRMS (CI): *m*/*z* calcd for $C_{17}H_{22}N_2O_3$ $(M)^+$: 302.1625; found: 302.1626.

UV (DMSO): $\lambda_{max}$ (abs) = 356 nm; $\lambda_{max}$ (em) = 412 nm.

### 7-(*N*,*N*-Diethylamino)-4-(piperidin-1-yl)-2*H*-chromen-2-one (6b)

According to the general procedure for aminations, triflate **2** (73 mg, 0.20 mmol) was reacted with piperidine (24 µL, 20.7 mg, 0.24 mmol) and $Et_3N$ (55 µL, 40 mg, 0.4 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 98:2, 95:5, 9:1), **6b** was isolated as a yellow solid; yield: 59 mg (0.20 mmol, 98%); mp 100–101 °C; $R_f$ = 0.19 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.1 Hz, 6 H), 1.61–1.71 (m, 6 H), 3.12 (m, 4 H), 3.32 (q, *J* = 7.1 Hz, 4 H), 5.35 (s, 1 H), 6.40 (d, *J* = 2.6 Hz, 1 H), 6.47 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.30 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 24.4, 25.7, 44.6, 52.2, 91.9, 98.0, 105.0, 107.7, 125.9, 150.0, 156.6, 162.8, 164.0.

HRMS (CI): *m*/*z* calcd for $C_{18}H_{24}N_2O_2$ $(M)^+$: 300.1832; found: 300.1838.

UV (DMSO): $\lambda_{max}$ (abs) = 362 nm; $\lambda_{max}$ (em) = 430 nm; $\Phi_F$ = 0.64.

Anal. Calcd for $C_{18}H_{24}N_2O_2$ (300.40): C, 71.97; H, 8.05, N, 9.33. Found: C, 71.99; H, 8.27; N, 9.04.

### 4,7-Bis(*N*,*N*-diethylamino)-2*H*-chromen-2-one (6c)

According to the general procedure for aminations, triflate **2** (73 mg, 0.20 mmol) was treated with $Et_2NH$ (25 µL, 17.6 mg, 0.24 mmol) and $Et_3N$ (55 µL, 40 mg, 0.4 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 9:1), **6c** was isolated as a yellow oil; yield: 39 mg (0.14 mmol, 68%); $R_f$ = 0.19 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 6 H), 1.20 (t, *J* = 7.1 Hz, 6 H), 3.34 (q, *J* = 7.1 Hz, 4 H), 3.37 (q, *J* = 7.1 Hz, 4 H), 5.34 (s, 1 H), 6.45 (d, *J* = 2.6 Hz, 1 H), 6.50 (dd, *J* = 9.1, 2.7 Hz, 1 H), 7.40 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.2, 12.4, 44.5, 45.3, 90.6, 98.1, 105.0, 107.4, 126.0, 149.8, 156.6, 160.0, 163.8.

HRMS (CI): *m*/*z* calcd for $C_{17}H_{24}N_2O_2$ $(M)^+$: 288.1832; found: 288.1841.

UV (DMSO): $\lambda_{max}$ (abs) = 352 nm; $\lambda_{max}$ (em) = 417 nm.

### 4-(*N*,*N*-Dibenzylamino)-7-(*N*,*N*-diethylamino)-2*H*-chromen-2-one (6d)

According to the general procedure for aminations, triflate **2** (73 mg, 0.20 mmol) was reacted with dibenzylamine (46 µL, 47 mg, 0.24 mmol) and $Et_3N$ (55 µL, 40 mg, 0.40 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 9:1), **6d** was isolated as a pale brown solid; yield: 50 mg (0.12 mmol, 60%); mp 100–101 °C; $R_f$ = 0.1 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.1 Hz, 6 H), 3.31 (q, *J* = 7.1 Hz, 4 H), 4.42 (s, 4 H), 5.32 (s, 1 H), 6.40–6.45 (m, 2 H), 7.15–7.28 (m, 10 H), 7.51 (d, *J* = 8.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 44.6, 55.2, 93.2, 98.2, 104.6, 107.9, 125.8, 127.5, 127.5, 128.7, 136.3, 150.1, 156.8, 160.6, 163.5.

HRMS (CI): *m*/*z* calcd for $C_{27}H_{28}N_2O_2$ $(M)^+$: 412.2145; found: 412.2161.

UV (DMSO): $\lambda_{max}$ (abs) 356 nm; $\lambda_{max}$ (em) = 418 nm.

Anal. Calcd $C_{27}H_{28}N_2O_2$ (412.53): C, 78.61; H, 6.84; N, 6.79. Found: C, 78.99; H, 6.96; N, 6.69.

### 7-(*N*,*N*-Diethylamino)-4-{[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*-methylamino}-2*H*-chromen-2-one (6e)

According to the general procedure for aminations, triflate **2** (73 mg, 0.20 mmol) was reacted with ephedrine (40 mg, 0.24 mmol) and $Et_3N$ (55 µL, 40 mg, 0.4 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 9:1), **6e** was isolated as a yellow solid; yield: 42 mg (0.11 mmol, 56%); mp 100–102 °C; $R_f$ = 0.1 ($CH_2Cl_2$–MeOH 95:5).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 6 H), 1.51 (d, *J* = 6.7 Hz, 3 H), 2.44 (br s, 1 H), 2.82 (s, 3 H), 3.38 (q, *J* = 7.1 Hz, 4 H), 4.26 (dq, *J* = 6.9, 6.7 Hz, 1 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 4.91 (s, 1 H), 6.40 (d, *J* = 2.6 Hz, 1 H), 6.44 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.14–7.25 (m, 6 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 13.5, 33.4, 44.5, 61.9, 76.5, 90.5, 98.0, 104.6, 107.3, 126.1, 126.3, 128.4, 141.7, 149.8, 156.4, 161.5, 163.7.

HRMS (CI): *m*/*z* calcd for $C_{23}H_{29}N_2O_3$ $(M + H)^+$: 381.2173; found: 381.2164.

UV (DMSO): $\lambda_{max}$ (abs) = 351 nm; $\lambda_{max}$ (em) = 410 nm.

### 7-(*N*,*N*-Diethylamino)-2-oxo-2*H*-chromen-4-yl-(*S*)-leucine Methyl Ester (6f)

According to the general procedure for aminations, triflate **2** (73 mg, 0.20 mmol) was reacted with (*S*)-leucine methyl ester hydrochloride (44 mg, 0.24 mmol) and $Et_3N$ (110 µL, 80 mg, 0.80 mmol). After workup and column chromatography (silica gel, $CH_2Cl_2$–EtOAc 95:5), **6f** was isolated as a yellow solid; yield: 45 mg (0.12 mmol, 62%); mp 198–200 °C; $R_f$ = 0.51 ($CH_2Cl_2$–EtOAc 9:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.2 Hz, 3 H), 0.96 (d, *J* = 6.2 Hz, 3 H), 1.17 (t, *J* = 7.1 Hz, 6 H), 1.69–1.82 (m, 3 H), 3.31–3.41 (m, 4 H), 3.79 (s, 3 H), 4.18 (td, *J* = 7.7, 6.1 Hz, 1 H), 4.98 (s, 1 H), 5.82 (d, *J* = 7.9 Hz, 1 H), 6.29 (d, *J* = 2.5 Hz, 1 H), 6.42 (dd, *J* = 9.0 2.5 Hz, 1 H), 7.23 (d, *J* = 9.1 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.5, 21.9, 22.7, 25.0, 41.0, 44.6, 52.7, 53.8, 80.9, 97.8, 102.2, 107.8, 121.5, 150.5, 153.3, 155.6, 164.1, 174.2.

HRMS (CI): *m*/*z* calcd for $C_{20}H_{29}N_2O_4$ $(M + H)^+$: 361.2122; found: 361.2120.

UV (DMSO): $\lambda_{max}$ (abs) = 345 nm; $\lambda_{max}$ (em) = 390 nm.

Anal. Calcd for $C_{20}H_{28}N_2O_4$ (360.45): C, 66.64; H, 7.83; N, 7.77. Found: C, 66.54; H, 8.18; N, 7.47.

### 4-[(2,6-Dichlorophenyl)thio]-7-(*N*,*N*-diethylamino)-2*H*-chromen-2-one (7a)

In analogy to the general procedure for aminations, triflate **2** (183 mg, 0.50 mmol) was reacted with 2,6-dichlorothiophenol (89.5 mg, 0.50 mmol) and $Et_3N$ (140 µL, 103 mg, 1.0 mmol). The reaction mixture was stirred at r.t. for 24 h. After workup as usual, the crude product was crystallized from $Et_2O$–PE to provide **7a** as a brown solid; yield: 190 mg (0.485 mmol, 97%); mp 154–155 °C; $R_f$ = 0.73 ($CH_2Cl_2$–MeOH 95:5).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 6 H), 3.42 (q, *J* = 7.1 Hz, 4 H), 5.15 (s, 1 H), 6.48 (d, *J* = 2.5 Hz, 1 H), 6.62 (dd, *J* = 9.0, 2.8 Hz, 1 H), 7.39 (m, 1 H), 7.52 (m, 2 H), 7.64 (d, *J* = 9.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 12.4, 44.8, 97.4, 101.5, 106.5, 108.5, 124.8, 126.2, 129.3, 132.3, 142.2, 150.9, 153.5, 154.9, 160.6.

HRMS (CI): *m*/*z* calcd for $C_{19}H_{17}Cl_2NO_2S$ $(M)^+$: 393.0357; found: 393.0357.

UV (DMSO): $\lambda_{max}$ (abs) = 385 nm; $\lambda_{max}$ (em) = 503 nm; $\Phi_F$ = 0.63.

### *N*-Acetyl-*S*-[7-(*N*,*N*-diethylamino)-2-oxo-2*H*-chromen-4-yl]-(*R*)-cysteine (7b)

Triflate **2** (73 mg, 0.20 mmol), *N*-acetyl-(*R*)-cysteine (98 mg, 0.60 mmol), and $Et_3N$ (55 µL, 40 mg, 0.4 mmol) were dissolved in a 7:3 $H_2O$–1,4-dioxane mixture (1 mL) and the mixture was allowed to stir overnight at r.t. The solution was adjusted to pH 3 with aq 1 N $KHSO_4$ before it was extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were dried (anhyd $MgSO_4$), concentrated in vacuo, and purified by flash chromatography (silica gel, $CH_2Cl_2$–MeOH–AcOH 94:5:1) to provide **7b** as a colorless solid; yield: 60 mg (0.16 mmol, 80%); mp 106–108 °C; $R_f$ = 0.35 ($CH_2Cl_2$–MeOH–AcOH 91:8:1).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.11 (t, *J* = 6.9 Hz, 6 H), 1.86 (s, 3 H), 3.30 (dd, *J* = 13.6, 8.5 Hz, 1 H), 3.41 (q, *J* = 6.8 Hz, 4 H), 3.52 (dd, *J* = 13.4, 4.4 Hz, 1 H), 4.53 (m, 1 H), 5.95 (s, 1 H), 6.49 (d, *J* = 1.8 Hz, 1 H), 6.69 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 12.3, 22.3, 31.4, 44.0, 50.9, 96.6, 100.3, 105.9, 108.7, 124.7, 150.7, 154.2, 155.1, 159.0, 169.6, 171.4.

HRMS (CI): *m*/*z* calcd for $C_{18}H_{21}N_2O_4S$ $(M - OH)^+$: 361.1217; found: 361.1224.

UV (DMSO): $\lambda_{max}$ (abs) = 382 nm; $\lambda_{max}$ (em) = 482 nm.

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## Supporting Information

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