

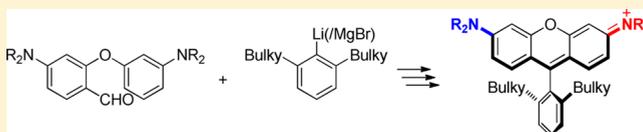
# Synthesis of Sterically Protected Xanthene Dyes with Bulky Groups at C-3' and C-7'

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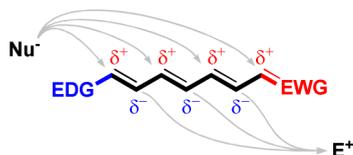
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**S** Supporting Information

**ABSTRACT:** Substitution of the xanthene scaffold with bulky groups at C-3' and C-7' is expected to protect the electrophilic central methine carbon against nucleophilic attack and inhibit stacking. However, such structures are not readily prepared via traditional xanthene syntheses. We have devised an alternative and convenient synthesis to enable facile preparation of this subset of xanthene dyes under mild conditions and in good yields.



An electronic push–pull system displays a narrow HOMO–LUMO band gap and enables absorption in the visible and even longer-wavelength spectral region.<sup>1</sup> Many different classes of small-molecule organic dyes have been constructed following this principle and found broad applications. However, this conjugated backbone is polarized and becomes intrinsically reactive toward both nucleophiles and electrophiles (Figure 1). While this reactivity has been

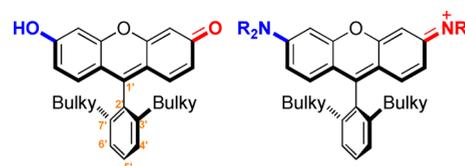


**Figure 1.** Generic push–pull scaffold that is routinely found in a small-molecule organic fluorophore.

harnessed as a modulation mechanism<sup>2</sup> of the absorption and fluorescence properties of a fluorophore in designing a molecular probe or sensor, it is generally considered a limitation.

Steric protection has been routinely employed in physical organic chemistry to render a thermodynamically reactive species kinetically persistent.<sup>3</sup> Based on this idea, polymethine dyes were threaded into various macrocycles for improved chemostability.<sup>4</sup> However, such supramolecular inclusion complexes are typically large in size, and their syntheses are not as convenient as small-molecule dyes. Bulky groups rationally installed onto the fluorophore scaffold could serve as a molecular alternative to the aforementioned supramolecular approach, providing sufficient protection to the push–pull backbone with minimal structural cost. Protection of an organic dye with sterics is a routine practice in material sciences in any solid-state application to minimize dye aggregations.<sup>5</sup> Xanthenes are well-accepted bright fluorescent dyes and are also known to have poor chemostability toward nucleophilic attack at the central methine carbon atom, that is,

C-1' (Figure 2).<sup>6</sup> Installation of bulky groups on the C-3' and C-7' is expected to block the trajectories of an incoming

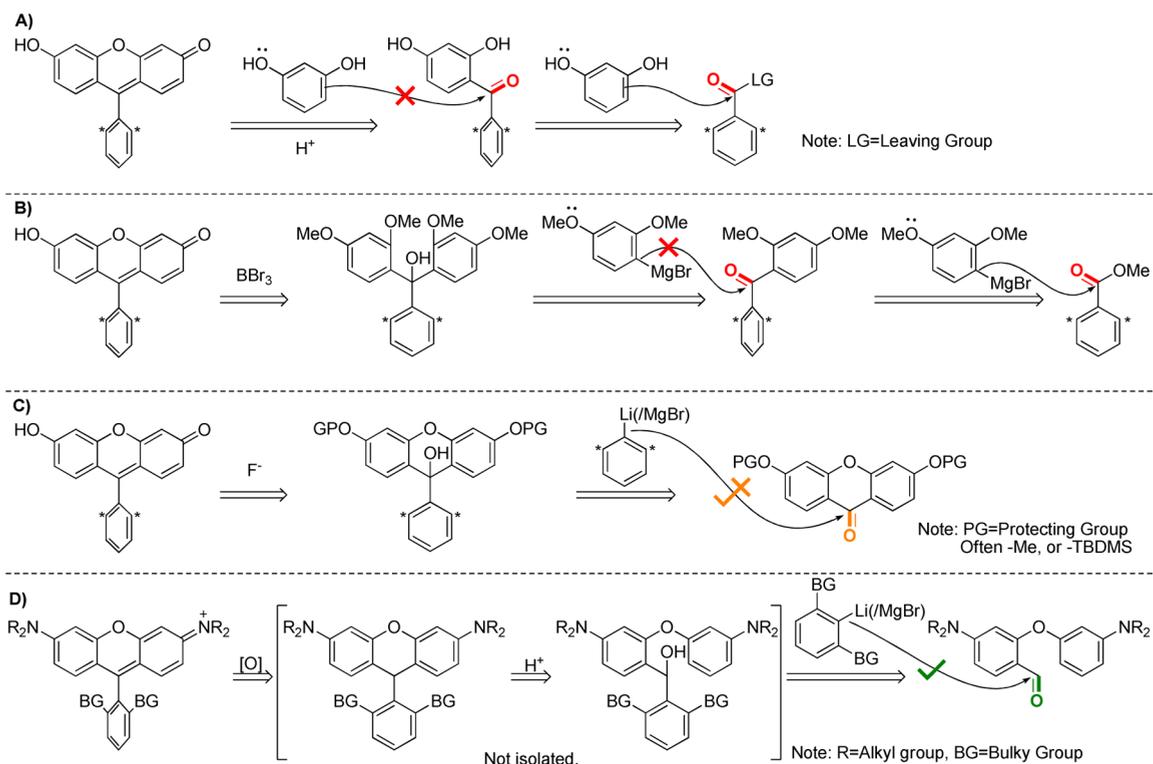


**Figure 2.** Structures of the C-3'- and C-7'-disubstituted xanthene dyes.

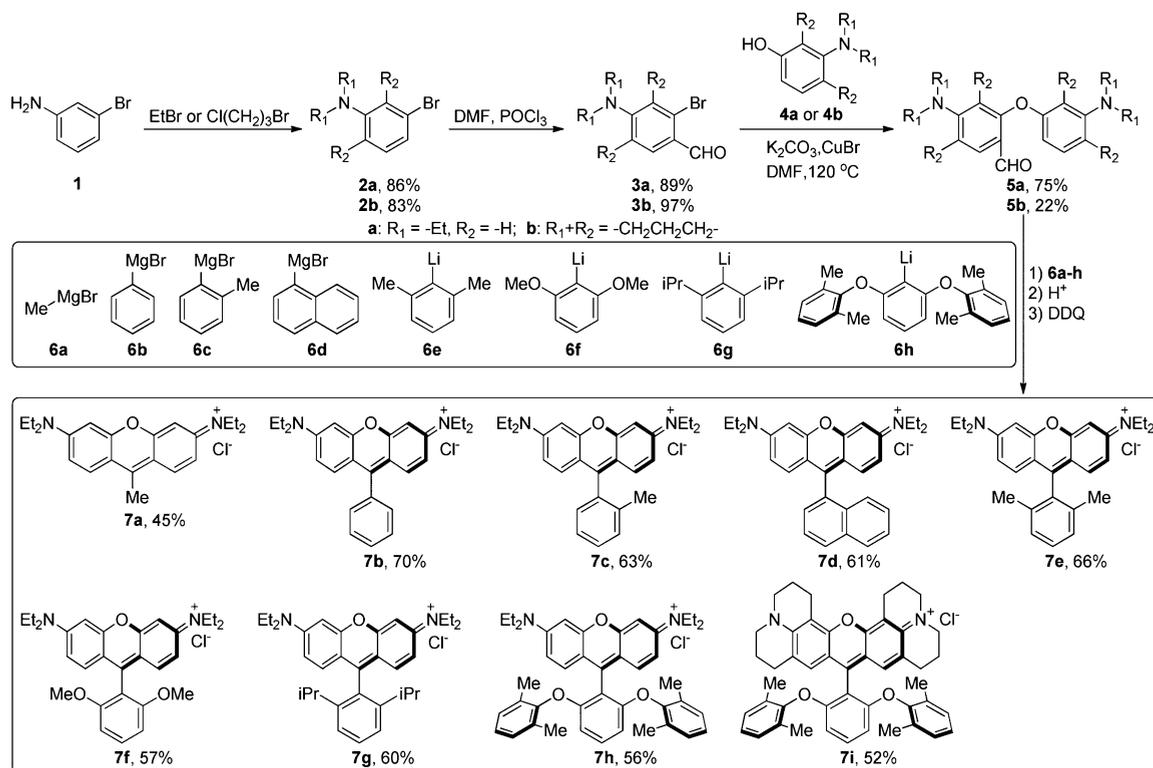
nucleophile to attack the central methine carbon. However, such scaffolds are not readily synthesized via existing xanthene syntheses, and we herein report a novel and convenient method to address this need.

Xanthenes are traditionally synthesized via acid-catalyzed condensation between a benzophenone, typically generated in situ, with electron-rich aromatics (Figure 3A).<sup>7</sup> An alternative synthesis (Figure 3B), a two-step cascade starting from a phenyl magnesium bromide and an aromatic ester, was achieved by Strongin et al. by employing Grignard chemistry.<sup>8</sup> However, both methods are not suitable for preparation of 3'- and 7'-disubstituted xanthenes because the presence of two bulky groups in close proximity (at starred positions in Figure 3) renders the electrophilic carbonyl group inaccessible for a nucleophile from either face. Another synthesis of xanthene dyes involves the nucleophilic addition of an aromatic Grignard (or lithium) reagent to a xanthone (Figure 3C).<sup>9</sup> The carbonyl group of this xanthone is more accessible compared to the benzophenones in the first two methods. However, the planarity of this molecule facilitates electron delocalization to this carbonyl, and therefore, it is comparatively less electrophilic and less reactive toward nucleophilic attack. Xanthenes with two methyl<sup>9f</sup> or methoxyl groups<sup>9d</sup> at C-3' and C-7' were

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**Figure 3.** Existing syntheses (A–C) and our proposed synthesis (D) of xanthene dyes. The electrophilic carbonyl group is more sterically accessible as the coded color changes from red to orange to green.



**Figure 4.** Synthesis of rhodamine-type xanthene dyes (7a–i) with or without bulky groups at C-3' and C-7'.

synthesized by this method in generally good yields but not with bulkier functional groups. Therefore, a novel method that allows convenient preparation of otherwise difficult-to-attain, if at all, 3'- and 7'-disubstituted xanthene dyes is a viable addition to the field. The retrosynthetic analysis of our proposed

method is shown in [Figure 3D](#), with rhodamine-type dyes as an example. The key step of this cascade is the nucleophilic addition of a 2,6-disubstituted phenyl lithium (or magnesium bromide) to an appropriately functionalized benzaldehyde, whose carbonyl group is not only more reactive compared to

the carbonyl group of the various benzophenones used in the previous three existing xanthene syntheses but also more sterically accessible. This rationalizes why it readily reacts with very hindered nucleophiles (vide infra). The resulting secondary alcohol is treated with acid to induce the cyclization via an intramolecular electrophilic aromatic substitution to generate a triarylmethane, which is oxidized spontaneously or chemically to furnish the desired 3',7'-disubstituted xanthenes.

Syntheses of such xanthene dyes with substitutions at both C-3' and C-7' are detailed in Figure 4. 3-Bromoaniline (**1**) is alkylated with EtI or 3-chlorobromopropane to afford compounds **2a,b**. Compounds **2a,b** are readily formylated to give **3a,b** nearly quantitatively via Vilsmeier–Haack reagent at room temperature in CH<sub>2</sub>Cl<sub>2</sub>. Nucleophilic aromatic substitution of the bromine atom of compound **3a** by 3-diethylaminophenol (**4a**) under Ullmann conditions yielded the prefunctionalized benzaldehyde **5a**<sup>10</sup> in a 75% yield. Compound **5b** was prepared analogously from condensation between **3b** and **4b** in a 22% yield. Then, the benzaldehydes **5a,b** were reacted with a number of alkyl Grignard reagents, aryl Grignard reagents, or aryl lithium reagents, some of which (**6e–h**) are very sterically hindered, in a liquid N<sub>2</sub>/EtOAc bath. The reaction occurred smoothly at –78 °C and was completed in less than 10 min based on TLC monitoring. The resulting secondary alcohols were not isolated or purified by any means. Instead, into the reaction flask was added dilute HCl solution. Upon heating the resulting mixture to 50 °C for 15 min, the secondary alcohol intermediate was converted to the corresponding triarylmethane analogues quantitatively. The crude triarylmethanes in CH<sub>2</sub>Cl<sub>2</sub>, from a liquid–liquid extraction, were not stable and spontaneously oxidized if not protected from air. They were also readily oxidized with addition of DDQ. Pure xanthene dyes (**7a–i**) were obtained with a flash column typically in an overall yield of over 50% starting from aldehydes **5a,b**.

This method is also suitable for preparation of 3',7'-disubstituted fluorescein-type xanthene dyes (Figure 5). Since

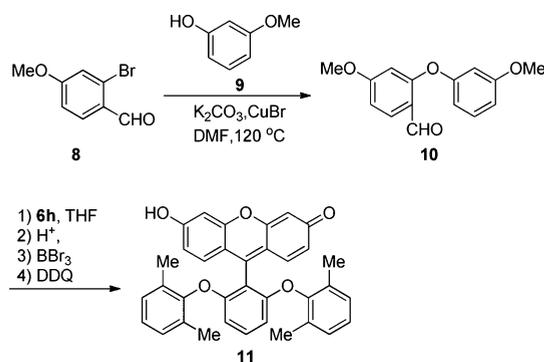


Figure 5. Synthesis of fluorescein-type xanthene dyes with bulky groups at C-3' and C-7.

the syntheses of the dimethyl-<sup>9d</sup> or dimethoxyl<sup>11</sup>-substituted analogues have been reported elsewhere, only the most bulky lithium reagent **6h** was reacted with **10** to showcase the capability of this method. This synthesis is analogous to the aforementioned synthesis of the rhodamine series (**7a–i**), except that an extra demethylation step is needed before oxidation. Compound **11** was obtained in an overall yield of 74% from compound **8**.

The UV–vis absorption and fluorescence properties of these new dyes (**7e–i** and **11**) were studied (Table 1 and Figure S2).

Table 1. Spectroscopic Properties of Dye **7e–i** and **11**

dyes	abs (nm)	em (nm)	$\epsilon$ (M <sup>-1</sup> cm <sup>-1</sup> )	$\phi$
<b>7e</b>	558	581	120000	0.48 <sup>a</sup>
<b>7f</b>	558	578	61000	0.51 <sup>a</sup>
<b>7g</b>	558	582	45000	0.29 <sup>a</sup>
<b>7h</b>	562	583	75000	0.48 <sup>a</sup>
<b>7i</b>	583	601	107000	0.57 <sup>a</sup>
<b>11</b>	510	528	63000	0.91 <sup>b</sup>

<sup>a</sup>In EtOH, with rhodamine B (0.49 in EtOH<sup>12</sup>) as a reference. <sup>b</sup>In 0.1 M NaOH solution with 5% EtOH, with fluorescein (0.95 in 0.1 M NaOH<sup>13</sup>) as a reference.

Rhodamine-type dyes (**7e–h**) display an absorption band with a maximum at ca. 560 nm and emit at 580 nm in EtOH, regardless of the nature of steric group substituted at C-3' and C-7'. The molar absorptivity of rhodamines decreases as the sizes of the groups at C-3' and C-7' increase. The fluorescence quantum yield of **7g** is low at 0.29, while others are higher at ca. 0.5. In comparison, **7i** is a longer-wavelength and brighter dye than **7e–h**. The molar absorptivity of **7i** is notably higher. Compound **11** in 0.1 M NaOH solution containing 5% EtOH absorbs maximally at 510 nm ( $\epsilon = 63\,000\text{ M}^{-1}\text{ cm}^{-1}$ ) and emits at 528 nm with a fluorescence quantum yield of 0.91. As expected, these dyes were found to not aggregate even at 0.1 mM in H<sub>2</sub>O/EtOH (95:5, v/v) as showcased with **7h** and **7i**. High chemostability of these dyes was showcased with **7h** and **7i**, with **7c** as a negative control (Figure S2). The absorption spectrum of a solution of **7h** and **7i** in EtOH was not affected upon addition of 10  $\mu\text{L}$  of NaOH solution (20 wt %). In comparison, the stereotypical purple color of a solution of **7c** completely disappeared with addition of the same amount of NaOH.

In summary, we have described a mild synthesis of sterically protected xanthene dyes, which are not readily attainable via other methodologies. This synthesis is complementary to all existing methods in that it allows preparation of xanthene dyes with bulky groups at both C-3' and C-7'. This method is also very versatile. Ethyl groups on the nitrogen atoms of aldehyde **3** may be replaced by any alkyl groups, as long they are compatible to lithium/Grignard chemistry. Also, other lithium or Grignard reagents can replace the sterically hindered lithium reagents used in this paper, depending on the structure of targeted xanthene dyes. Another merit of this synthesis is that the involved reaction conditions are very mild and purification is convenient.

## EXPERIMENTAL SECTION

**3-Bromo-*N,N*-diethylaniline (2a).** 3-Bromoaniline (50 g, 1 equiv, 0.29 mol), EtI (99.7 g, 2.2 equiv, 0.64 mol), K<sub>2</sub>CO<sub>3</sub> (40 g, 1 equiv, 0.29 mol), and anhydrous MeCN (300 mL) were added into a 1 L flask. The resulting mixture was heated to 80 °C with rigorous stirring for 24 h before being cooled to room temperature. Solid materials were filtered off using a Celite cake under vacuum and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was evaporated under reduced pressure to give the crude product as a brownish-orange liquid, which was purified via vacuum distillation (bp 90 °C at 90 Pa) to give **2a** (57 g, a colorless liquid) in an 86% yield: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.07 (dd, *J* = 8.2, 7.9 Hz, 1H), 6.82 (t, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 7.9 Hz, 2.0 Hz, 1H), 6.60 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 3.35 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H).

**8-Bromo-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinolone (2b).** 3-Bromoaniline (50 g, 1 equiv, 0.29 mol), excess 3-chlorobromopropane (200 g, 1.27 mol), and  $K_2CO_3$  (80 g, 2 equiv, 0.58 mol) were added into a 1 L flask. The resulting mixture was heated to 140 °C for 48 h with rigorous stirring before being cooled to room temperature.  $CH_2Cl_2$  (200 mL) was added to dilute the viscous mixture before all solid materials were filtered off.  $CH_2Cl_2$  was removed under reduced pressure. The resulting liquid, which is a solution of **2b** in 3-chlorobromopropane, was distilled under vacuum. Compound **2b** (bp 110 °C at 90 Pa) was obtained after 3-chlorobromopropane. Compound **2b** (63 g, a colorless liquid) was obtained in an 83% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.75 (d,  $J$  = 8.2 Hz, 1H), 6.64 (d,  $J$  = 8.2 Hz, 1H), 3.55 (t,  $J$  = 6.0 Hz, 4H), 3.14–3.08 (m, 4H), 2.76 (t,  $J$  = 6.0 Hz, 2H), 2.69 (t,  $J$  = 6.0 Hz, 2H), 2.38–2.32 (m, 2H), 1.98–1.93 (m, 4H).

**2-Bromo-4-(diethylamino)benzaldehyde (3a).**  $POCl_3$  (4.5 mL) and DMF (60 mL) were stirred together in a flask for 30 min at 0 °C before a solution of **2a** (20 g, 43.8 mmol) in anhydrous DMF (40 mL) was added slowly. The resulting mixture was stirred at room temperature for 6 h before being poured into ice water. Brownish-yellow precipitates were collected via a suction filtration and washed with water. The solid was dissolved back into  $CH_2Cl_2$ . Residual  $H_2O$  was removed with anhydrous  $MgSO_4$ . Upon suction filtration to remove solids, the filtrate was passed through a short silica column to remove the colored impurities. Evaporation under vacuum afforded **3a** (20.7 g, 89%) as a yellow crystalline solid:  $^1H$  NMR (400 MHz,  $CCl_3D$ )  $\delta$  10.05 (s, 1H), 7.77 (d,  $J$  = 8.9 Hz, 1H), 6.77 (s, 2H), 6.60 (d,  $J$  = 8.9 Hz, 1H), 3.42 (q,  $J$  = 6.9 Hz, 4H), 1.22 (t,  $J$  = 6.9 Hz, 6H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  189.9, 152.6, 131.3, 130.1, 121.5, 114.3, 110.2, 44.8, 12.4; EI-MS ( $m/z$ ) [ $M$ ] $^+$  calcd for  $C_{11}H_{14}BrNO$  255.01, found 255.0.

**8-Bromo-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinoline-9-carbaldehyde (3b).**  $POCl_3$  (11 mL) and DMF (120 mL) were stirred together in a flask for 30 min at 0 °C before a solution of **2b** (20 g, 79 mmol) in anhydrous DMF (20 mL) was added slowly. The reaction was carried out and worked up analogously to **3a**. Compound **3b** (21.6 g, 97%) was obtained as a yellow crystalline solid: mp 107.6–108.2 °C;  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  10.08 (s, 1H), 7.40 (s, 1H), 3.24–3.30 (m, 4H), 2.82 (t,  $J$  = 6.4 Hz, 2H), 2.69 (t,  $J$  = 6.4 Hz, 2H), 1.98–1.90 (m, 4H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  190.9, 148.9, 129.6, 128.3, 121.4, 119.7, 119.2, 77.4, 77.1, 76.8, 50.2, 49.8, 28.1, 27.4, 21.1, 21.0; HRMS (EI $^+$ ) [ $M$ ] $^+$  calcd for  $C_{13}H_{14}BrNO$  279.0259, found 279.0261.

**4-(Diethylamino)-2-(3-(diethylamino)phenoxy)benzaldehyde (5a).** Synthesis and characterizations were reported elsewhere.<sup>10</sup>

**8-((1,2,3,5,6,7-Hexahydropyrido[3,2,1-*ij*]quinolin-8-yl)oxy)-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinoline-9-carbaldehyde (5b).** Compounds **3b** (500 mg, 1 equiv, 1.78 mmol), **4b** (506 mg, 1.5 equiv, 2.68 mmol),  $K_2CO_3$  (369.8 mg, 1.5 equiv, 2.68 mmol),  $CuBr$  (26 mg, 0.1 equiv, 0.18 mmol), and DMF (40 mL) were added into a flask. The reaction mixture was thoroughly deoxygenated by bubbling Ar for 15 min, heated to 140 °C with rigorous stirring for 6 h, and cooled to room temperature. A saturated solution of  $NH_4Cl$  (50 mL) was added, and the resulting mixture was extracted repeatedly with  $CH_2Cl_2$ . The organic layer was combined, dried with  $MgSO_4$ , and filtered. Both  $CH_2Cl_2$  and DMF were removed under reduced pressure to yield a viscous residue, which was purified by a flash column using a mixture of petroleum ether and EtOAc [20:1, v/v] as an eluent to afford **5b** (153 mg) as a yellow solid in a 22% yield: mp 209.7–210.2 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.77 (s, 1H), 7.42 (s, 1H), 6.57 (d,  $J$  = 8.3 Hz, 1H), 6.68 (d,  $J$  = 8.3 Hz, 1H), 3.28 (t,  $J$  = 5.6 Hz, 2H), 3.23 (t,  $J$  = 5.6 Hz, 2H), 3.13 (q,  $J$  = 5.6 Hz, 4H), 2.88 (t,  $J$  = 6.4 Hz, 2H), 2.75 (t,  $J$  = 6.4 Hz, 2H), 2.68 (t,  $J$  = 6.4 Hz, 2H), 2.05–2.00 (m, 2H), 1.99–1.93 (m, 4H), 1.87–1.81 (m, 2H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  187.8, 155.3, 155.2, 149.1, 144.0, 126.5, 126.1, 117.8, 117.3, 115.3, 112.7, 109.1, 101.1, 50.1, 50.1, 49.7, 49.6, 27.4, 27.2, 22.3, 21.7, 21.4, 21.4, 20.8, 20.6; ESI-MS ( $m/z$ ) [ $M$  + Na] $^+$  calcd for  $C_{23}H_{28}N_2O_2Na$  411.2047, found 411.2047.

**2-Methylphenylmagnesium Bromide (6c).** This Grignard reagent as its THF solution was prepared by treatment of 2-methylbromobenzene with  $I_2$ -activated Mg powder in anhydrous THF.

**Naphthalen-1-ylmagnesium Bromide (6d).** This Grignard reagent as its THF solution was prepared by treatment of 1-bromonaphthalene with  $I_2$ -activated Mg powder in anhydrous THF.

**(2,6-Dimethylphenyl)lithium (6e).** A solution of *n*-BuLi (1.6 M in hexane) was syringed into a solution of 2-bromo-*m*-xylene in THF at –78 °C dropwise, and the resulting mixture was stirred for another 30 min prior to use.

**(2,6-Dimethoxyphenyl)lithium (6f).** A solution of *n*-BuLi (1.6 M in hexane) was syringed into a solution of 1,3-dimethoxybenzene in THF at 0 °C dropwise, and the resulting mixture was stirred for another 1 h prior to use.

**(2,6-Diisopropylphenyl)lithium (6g).** A solution of *n*-BuLi (1.6 M in Hexane) was syringed into a solution of 2-bromo-1,3-diisopropylbenzene in THF at –78 °C dropwise, and the resulting mixture was stirred for another 30 min prior to use.

**(2,6-Bis(2,6-dimethylphenoxy)phenyl)lithium (6h).** A solution of *n*-BuLi (1.6 M in hexane) was syringed into a solution of compound **12** in THF at 0 °C dropwise, and the resulting mixture was stirred for another 2 h prior to use.

**General Procedures for Rhodamine-Type Dyes (7a–h).** A solution of various lithium reagents (0.88 mmol, 1.5 equiv) in THF was added to a solution of compound **5a** (200 mg, 1 equiv, 0.59 mmol) in THF (40 mL) at –78 °C via syringe. The reaction mixture was allowed to warm to room temperature within 30 min. Dilute HCl solution (2 M, 50 mL) was poured into the reaction flask, and the resulting mixture was heated to 50 °C for 15 min with stirring. Upon being cooled to room temperature, the reaction mixture was extracted with  $CH_2Cl_2$  repeatedly. The combined organic layer was dried with anhydrous  $MgSO_4$  powder, and all solid was removed with a suction filtration. DDQ (134 mg, 1 equiv, 0.59 mmol) was added into the filtrate in one portion, and the mixture was stirred for 30 min at room temperature for the reaction to complete. Then, all  $CH_2Cl_2$  was removed under reduced pressure to give a viscous residue, from which compounds **7a–h** were obtained from a flash column over silica with a mixture of  $CH_2Cl_2$  and MeOH [95:5].

**N-(6-(Diethylamino)-9-methyl-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7a $^{14}$ ).** Compound **7a** (105 mg) was obtained as a red-violet solid in a 45% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.10 (d,  $J$  = 9.4 Hz, 2H), 7.12 (dd,  $J$  = 9.4, 1.6 Hz, 2H), 6.69 (d,  $J$  = 1.6 Hz, 2H), 3.63 (q,  $J$  = 6.9 Hz, 8H), 2.96 (s, 3H), 1.33 (t,  $J$  = 6.9 Hz, 12H).

**N-(6-(Diethylamino)-9-phenyl-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7b $^{15}$ ).** Compound **7b** (164 mg) was obtained as a violet solid in a 70% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.63–7.62 (m, 3H), 7.38–7.34 (m, 4H), 6.95 (dd,  $J$  = 9.6, 2.4 Hz, 2H), 6.87 (d,  $J$  = 2.4 Hz, 1H), 3.67 (q,  $J$  = 7.0 Hz, 8H), 1.34 (t,  $J$  = 7.0 Hz, 12H).

**N-(6-(Diethylamino)-9-(*o*-tolyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7c $^{16}$ ).** Compound **7c** (152 mg) was obtained as a violet solid in a 63% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.45 (t,  $J$  = 7.7 Hz, 1H), 7.38–7.32 (m, 2H), 7.12–7.07 (m, 3H), 6.90 (dd,  $J$  = 9.5, 2.2 Hz, 2H), 6.80 (d,  $J$  = 2.2 Hz, 2H), 3.62 (q,  $J$  = 7.1 Hz, 8H), 2.0 (s, 3H), 1.29 (t,  $J$  = 7.1 Hz, 12H).

**N-(6-(Diethylamino)-9-(naphthalen-1-yl)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7d $^{15}$ ).** Compound **7d** (160 mg) was obtained as a violet solid in a 61% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.08 (d,  $J$  = 8.2 Hz, 1H), 7.99 (d,  $J$  = 8.2 Hz, 1H), 7.56 (t,  $J$  = 7.1 Hz, 1H), 7.52 (d,  $J$  = 7.7 Hz, 1H), 7.38 (t,  $J$  = 8.0 Hz, 1H), 7.32 (d,  $J$  = 8.9 Hz, 1H), 7.05 (d,  $J$  = 9.5 Hz, 2H), 6.85 (d,  $J$  = 1.20 Hz, 2H), 6.74 (dd,  $J$  = 8.4, 2.0 Hz, 2H), 3.61–3.60 (m, 8H), 1.29–1.27 (m, 12H).

**N-(6-(Diethylamino)-9-(2,6-dimethylphenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7e).** Compound **7e** (165 mg) was obtained as a violet solid in a 66% yield. Compound **7e** decomposed before melting:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.36 (t,  $J$  = 7.6 Hz, 1H), 7.19 (d,  $J$  = 7.6 Hz, 2H), 7.07 (d,  $J$  = 9.4 Hz, 2H), 6.90 (dd,  $J$  = 9.4, 2.0 Hz, 2H), 6.85 (d,  $J$  = 2.0 Hz, 2H), 3.64 (q,  $J$  = 7.0

H<sub>2</sub>, 8H), 1.93 (s, 6H), 1.31 (t, *J* = 7.0 Hz, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.0, 157.9, 155.8, 135.6, 131.1, 131.0, 129.7, 128.0, 114.6, 113.1, 96.6, 46.2, 19.9, 12.7; EI-HRMS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>29</sub>H<sub>35</sub>N<sub>2</sub>O 427.2749, found 427.2751.

**N-(6-(Diethylamino)-9-(2,6-dimethoxyphenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7f).** Compound 7f (143 mg) was obtained as a violet solid in a 57% yield. Compound 7b decomposed before melting: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52 (t, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 2.4 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.61 (s, 6H), 3.58 (q, *J* = 6.8 Hz, 8H), 1.27 (t, *J* = 6.8 Hz, 12H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 158.2, 155.9, 155.8, 153.3, 149.9, 132.3, 131.6, 130.7, 129.2, 125.8, 114.5, 113.7, 108.0, 105.7, 96.5, 77.4, 77.1, 76.8, 46.3, 16.4, 12.7; ESI-HRMS (*m/z*) [*M* + *H*]<sup>+</sup> calcd for C<sub>29</sub>H<sub>35</sub>N<sub>2</sub>O<sub>3</sub> 459.2648, found 459.2646.

**N-(6-(Diethylamino)-9-(2,6-diisopropylphenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7g).** Compound 7g (172 mg) was obtained as a violet solid in a 60% yield. Compound 7c decomposed before melting: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.56 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 9.4 Hz, 2H), 6.98 (d, *J* = 2.2 Hz, 2H), 6.84 (dd, *J* = 9.3, 2.2 Hz, 2H), 3.66 (q, *J* = 7.2 Hz, 8H), 1.33 (t, *J* = 7.2 Hz, 12H), 1.26 (q, *J* = 6.8 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.7, 154.8, 146.6, 130.3, 129.5, 122.7, 113.3, 112.8, 96.9, 46.2, 30.4, 28.7, 23.4, 11.6; EI-HRMS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>33</sub>H<sub>43</sub>N<sub>2</sub>O 483.3375, found 483.3377.

**N-(9-(2,6-Bis(2,6-dimethylphenoxy)phenyl)-6-(diethylamino)-3H-xanthen-3-ylidene)-N-ethylethanaminium Chloride (7h).** Compound 7h (212 mg) was obtained as a violet solid in a 56% yield. Compound 7d decomposed before melting: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60 (d, *J* = 9.2 Hz, 2H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.01–6.98 (m, 8H), 6.85 (s, 2H), 6.19 (d, *J* = 8.4 Hz, 2H), 3.68–3.66 (m, 8H), 1.97 (s, 12H), 1.34–1.32 (m, 12H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 158.2, 155.9, 155.8, 153.3, 149.9, 132.3, 131.6, 130.7, 129.2, 125.8, 114.5, 113.7, 108.0, 105.7, 96.5, 77.4, 77.1, 76.8, 46.3, 16.5, 12.7. ESI-HRMS (*m/z*) [*M* + *H*]<sup>+</sup> calcd for C<sub>43</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub> 639.3587, found 639.3593.

**Compound 7i.** Compound 7i (96 mg) was obtained as a violet solid in a 52% yield starting from **5b** (100 mg) and **6h**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.12 (t, *J* = 8.4 Hz, 1H), 7.06 (s, 2H), 6.99–6.93 (m, 6H), 6.13 (d, *J* = 8.4 Hz, 2H), 3.53 (t, *J* = 4.2 Hz, 8H), 2.99 (t, *J* = 4.2 Hz, 4H), 2.72 (t, *J* = 4.2 Hz, 4H), 2.08–2.06 (m, 4H), 2.00–1.99 (m, 4H), 1.92 (s, 12H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.8, 152.5, 151.3, 150.0, 149.9, 131.8, 130.6, 129.1, 126.3, 125.6, 123.4, 113.6, 108.8, 105.5, 105.3, 77.5, 77.2, 76.8, 50.9, 50.5, 27.7, 20.8, 19.9, 19.7, 16.1; ESI-HRMS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>47</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub> 687.3587, found 687.3586.

**4-Methoxy-2-(3-methoxyphenoxy)benzaldehyde (10).** A 250 mL round-bottom flask was charged with 2-bromo-4-methoxybenzaldehyde (500 mg, 1 equiv, 2.33 mmol), 3-methoxyphenol (433 mg, 1.5 equiv, 3.49 mmol), K<sub>2</sub>CO<sub>3</sub> (482 mg, 1.5 equiv, 3.49 mmol), CuBr (33 mg, 0.1 equiv, 0.23 mmol), and DMF (40 mL). The reaction mixture was deoxygenated by bubbling Ar for 15 min before being heated to 140 °C with rigorous stirring for 6 h. Then the reaction was cooled to room temperature, and saturated NH<sub>4</sub>Cl solution (50 mL) was added. The resulting mixture was extracted repeatedly with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was combined, dried with MgSO<sub>4</sub>, and filtered. Both CH<sub>2</sub>Cl<sub>2</sub> and DMF were removed under reduced pressure to yield a viscous residue, which was purified by a flash column using a mixture of petroleum ether and EtOAc [20:1, v/v] as eluent to afford **10** (368 mg) as a colorless viscous residue in a 61% yield: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.33 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.63 (s, 1H), 6.38 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.9, 166.8, 161.7, 161.1, 157.4, 130.5, 130.2, 120.7, 111.5, 110.0, 109.7, 105.5, 103.7, 55.7, 55.5; EI-MS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>15</sub>H<sub>14</sub>O<sub>4</sub> 258.1; found 258.1.

**9-(2,6-Bis(2,6-dimethylphenoxy)phenyl)-6-hydroxy-3H-xanthen-3-one (11).** A solution of lithium reagent **6h** (1.2 mmol, 1.5 equiv) in THF was added to a solution of compound **10** (200 mg, 1 equiv, 0.77 mmol) in THF (40 mL) at –78 °C via syringe. The

reaction mixture was allowed to warm to room temperature within 30 min. Dilute HCl solution (2 M, 50 mL) was poured into the reaction flask, and the resulting mixture was heated to 50 °C for 15 min with stirring. Upon being cooled to room temperature, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> repeatedly. The combined organic layer was dried with anhydrous MgSO<sub>4</sub> powder, and all solid was removed with a suction filtration. Upon the filtrate being cooled to –78 °C with a liquid N<sub>2</sub>/EtOAc bath, BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL, 1 M, 3.0 equiv) was added with stirring. The mixture was allowed to warm to room temperature within 2 h before being quenched by slow addition of MeOH and then H<sub>2</sub>O. HBr fume was absorbed by a saturated NaHCO<sub>3</sub> solution by use of an inverted funnel. The reaction mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was combined, dried with anhydrous MgSO<sub>4</sub>, and filtered. DDQ (176 mg, 1.0 equiv, 0.77 mmol) was added into the filtrate in one portion, and the mixture was stirred for 30 min at room temperature for the reaction to complete. Then, all CH<sub>2</sub>Cl<sub>2</sub> was removed under reduced pressure to give a viscous residue, from which pure compound **11** (304 mg) as a red solid was obtained from a flash column over silica with a mixture of petroleum ether/EtOAc [1:2, v/v] in a 74% yield. Compound **11** decomposed before melting: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.29–7.03 (m, 11H), 6.20 (d, *J* = 7.6 Hz, 2H), 1.96 (s, 12H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 160.6, 157.2, 151.3, 134.1, 133.9, 132.0, 130.3, 127.1, 122.0, 118.3, 106.9, 104.1, 16.6; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 155.3, 149.4, 143.9, 132.0, 130.4, 130.0, 129.2, 125.7, 108.5, 105.1, 103.4, 15.7; EI-HRMS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>35</sub>H<sub>28</sub>O<sub>5</sub> 528.1937, found 528.1936.

**1,3-Bis(2,6-dimethylphenoxy)benzene (12).** 1,3-Dibromobenzene (500 mg, 1 equiv, 2.12 mmol), 2,6-dimethylphenol (777 mg, 3 equiv, 6.36 mmol), K<sub>2</sub>CO<sub>3</sub> (878 mg, 3 equiv, 6.36 mmol), CuBr (60 mg, 0.2 equiv, 0.42 mmol), and DMF (40 mL) were mixed in a flask. Upon deoxygenation by bubbling Ar for 20 min, the mixture was heated to 140 °C under Ar overnight. Then the reaction was cooled to room temperature, and saturated NH<sub>4</sub>Cl solution (50 mL) was added. The resulting mixture was extracted repeatedly with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was combined, dried with MgSO<sub>4</sub>, and filtered. Both CH<sub>2</sub>Cl<sub>2</sub> and DMF were removed under reduced pressure to yield a viscous residue, which was purified by a flash column using petroleum ether as eluent to afford **12** (403 mg) as a white crystalline solid in a 60% yield: mp 42.3–42.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.12–7.04 (m, 7H), 6.39–6.33 (m, 3H), 2.12 (s, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.4, 151.1, 131.4, 130.2, 129.0, 126.1, 107.5, 102.3, 16.4; EI-MS (*m/z*) [*M*]<sup>+</sup> calcd for C<sub>22</sub>H<sub>22</sub>O<sub>2</sub> 318.2, found 318.2.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01746.

General procedures, aggregation measurements, absorption, fluorescence, NMR, and MS spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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