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Synthesis of Spiropyrans As Building Blocks for Molecular Switches and Dyads

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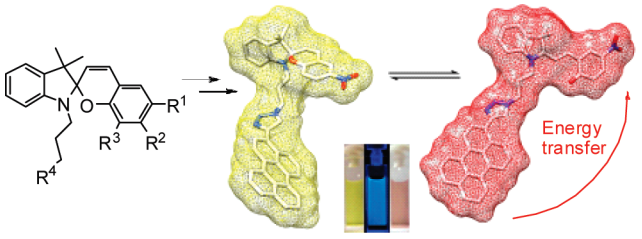

The synthesis of spiropyrans was improved significantly with use of ultrasonic radiation. To show the broad applicability of this methodology a range of spiropyrans were prepared which are equipped with iodo, hydroxyl, ethinyl, or azido groups as potential building blocks for conjugation to functional π-systems or biopolymers. Representatively, the conjugation chemistry was demonstrated for the preparation of spiropyran conjugates with pyrene, perylene, and nile red via the "click"-type cycloaddition. These molecular dyads were characterized by optical spectroscopy.

Photochromic switches have received increasing attention due to their potential as part of optoelectronic molecular devices,[1] sensors,[2] and fluorescent switches for photonic materials,[3] nanoparticles,[4] and labeling of biopolymers.[5] Among the structurally diverse photochromic compounds spiropyrans[6] and spirooxazines[6,7] play a special role since their photoinduced and reversible ring-opening to the corresponding merocyanines is accompanied not only by a significant structural change from a nonplanar to a planar structure but also by a large polarity increase. Hence it is not surprising that spiropyrans have not only been used for organic materials but also conjugated to amino acids,[8] peptides,[9] proteins,[10] and nucleic acids[11] in order to equip these biomolecules with the photochromic switch. Despite the great potential of spiropyrans, however, the synthetic accessibility of these compounds is rather limited. Herein, we want to present an improved synthetic procedure for spiropyrans that are equipped with iodo, hydroxyl, azido, or ethinyl groups. These spiropyrans represent building blocks that can be used for cross-linking reactions or bioconjugation to attach the photochromic compound to functional π-systems or biopolymers, respectively. Representatively, we demonstrate this for the preparation of spiropyran-chromophore conjugates as molecular dyads via "click"-type cycloaddition.

As building blocks we synthesized two sets of spiropyrans carrying either hydroxyl or iodo functionalities as reactive groups (Scheme 1). For the first set of spiropyrans, the alkylation of 2,3,3-trimethylindolenine (**1**) with 3-iodopropanol gave in good yield the corresponding indolium iodide **2** that carries the short C3-linker. Deprotonation of **2** with potassium hydroxide gave **3** as colorless crystals. The standard protocol for preparation of spiropyrans, which is refluxing **3** with 4-nitrosalicylaldehyde in EtOH, gave the spiropyran **4a** in only 16% yield after 3 h and in 54% yield after 24 h. Longer heating caused accumulation of side products that complicated the purification. It turned out to be very useful to use ultrasonic radiation for 1−2 h in EtOH[12] to obtain **4a** as well as the spiropyrans **4b**−**k** in acceptable to excellent yields ranging from 52% to 93%. We assume that ultrasound enhances reaction rates simply by a more intimate mixing of reagents as was observed for other organic reactions.[13] Using this significantly facilitated and efficiently working synthetic protocol we synthesized the second set of spiropyrans bearing an iodoalkyl linker. The indolenine **1** was first treated with 1,3-diiodopropane, and **5** was subsequently deprotonated to the methyleneindoline **6**. With use of ultrasonic radiation, the spiropyrans **7a**−**f** were obtained in good yields (58−94%). This method was also successfully applied to prepare spirooxazine **8**.

The synthesized spiropyrans **4a**−**k** and **7a**−**f** bear different substitution patterns at the phenolic part, including electron-withdrawing and -donating substituents (Table 1).

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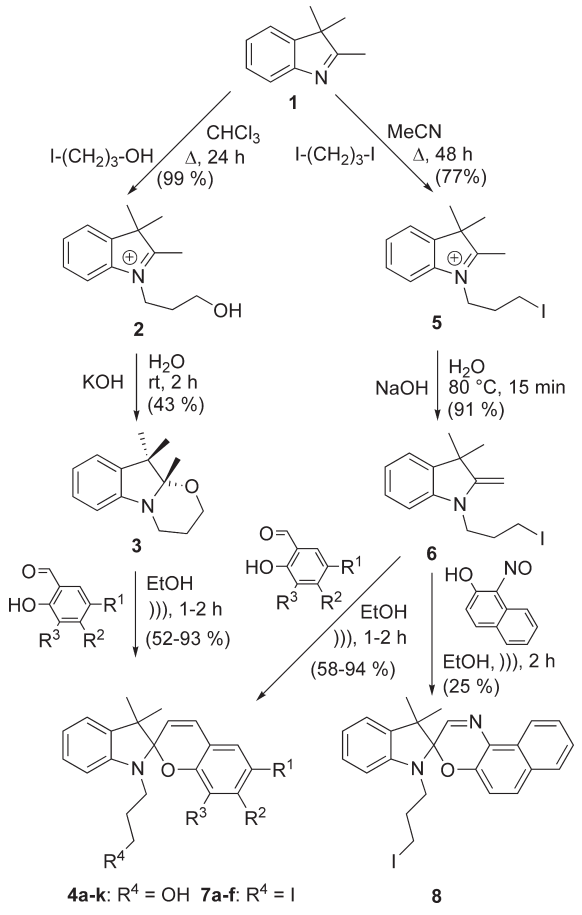
SCHEME 1. Synthesis of Spiropyran Building Blocks 4a−k and 7a−f and the Spirooxazine 8[a]



[a]For R^1, R^2, and R^3 see Table 1.

Accordingly, the photocoloration properties which were measured immediately after saturation of the merocyanines by irradiation at 312 nm differ quite significantly (Figure 1). As expected, the spiropyrans **4a** and **4i**, bearing a nitro group as R^1, showed the strongest extinction of the merocyanine at 549 or 568 nm, respectively. Moreover, we confirmed representatively for compounds **4a** and **4h** the reversibility of the photoinduced switching (see the Supporting Information).

Representatively, we tested with spiropyran **7a** the applicability of the synthesized building blocks. The Huisgen−Meldal−Sharpless "click" chemistry[14−16] was chosen as a facile methodology for the preparation of the chromophore−spiropyran conjugates **10a−c** as molecular dyads. Surprisingly, the application of this reaction has rarely been applied for spiropyran conjugation.[17] The spiropyran **7a** was first converted to the corresponding azide **9**, which was further

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TABLE 1. Substituents and Yields of Spiropyrans 4a−k and 7a−f

	R^1	R^2	R^3	yield (%)
4a	NO_2	H	H	84
4b	H	H	H	87
4c	Cl	H	H	78
4d	OCH_3	H	H	54
4e	Br	H	Br	93
4f	C≡CH	H	H	68
4g	C≡CH	H	OCH_3	75
4h	Br	H	H	52
4i	NO_2	H	OCH_3	83
4j	Br	H	OCH_3	76
4k	H	OCH_3	H	82
7a	NO_2	H	H	94
7b	Cl	H	H	74
7c	Br	H	Br	83
7d	Br	H	OCH_3	80
7e	NO_2	H	OCH_3	68
7f	C≡CH	H	H	58

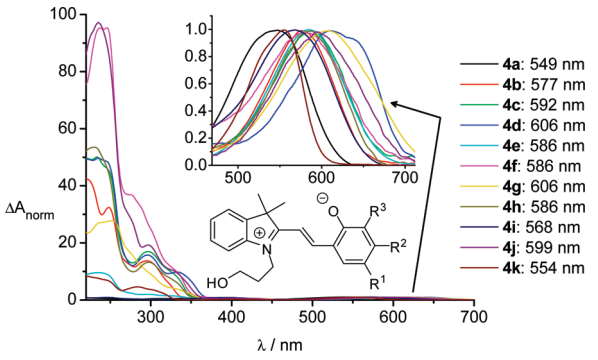
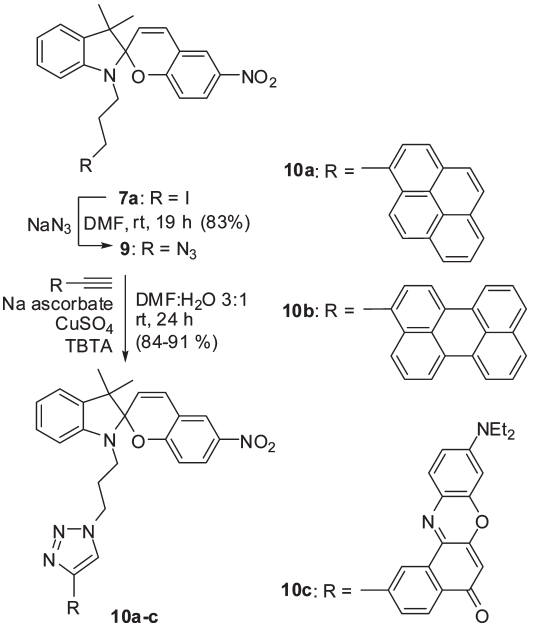


FIGURE 1. UV/vis absorption of the merocyanines **4a−k** (100 μM in EtOH, after irradiation at λ = 312 nm, for R^1, R^2, and R^3 see Table 1).

SCHEME 2. Synthesis of Spiropyran Dyads 10a−c



reacted in the Cu(I)-catalyzed cycloaddition to the conjugates **10a−c**, bearing pyrene, perylene, or nile red as chromophores, in excellent yields (84−91%) (Scheme 2).

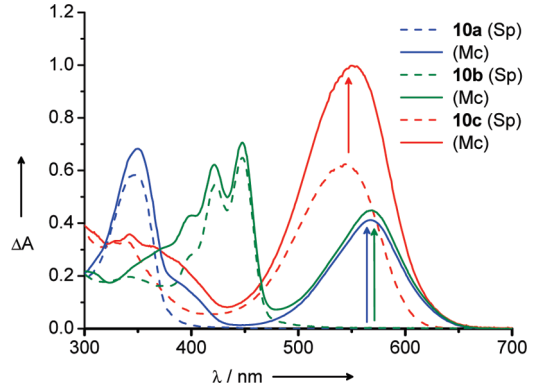


FIGURE 2. UV/vis absorption spectra of **10a**−**c** (100 μM in EtOH) after irradiation at 312 nm (solid lines, Mc) and after irradiation at 590 nm (dashed lines, Sp).

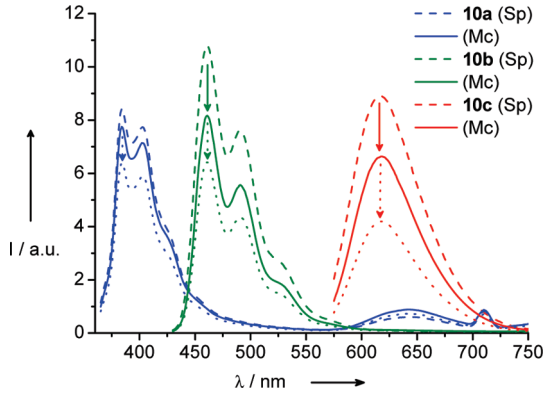


FIGURE 3. Fluorescence spectra of **10a**−**c** (100 μM in EtOH) after irradiation at 312 nm (solid lines, Mc) and after irradiation at 590 nm (dashed lines, Sp); λ_{exc} = 355 nm (**10a**), 413 nm (**10b**), 545 nm (**10c**). The dotted lines represent the spectra that are corrected by the differences in optical density at the excitation wavelength.

The UV/vis absorption of the spiropyran conjugates **10a**−**c** (Figure 2) after irradiation at 590 nm display exclusively the spiropyran isomer and the additional chromophore by the characteristic bands at ~350 (pyrene in **10a**), ~425 (perylene in **10b**), and ~550 nm (nile red in **10c**). After irradiation at 312 nm, the merocyanine forms of all three dyads show an additional absorption at ~560 nm. If the dyads are excited at their characteristic wavelength (**10a**: 355 nm; **10b**: 413 nm; **10c**: 545 nm) the fluorescence (Figure 3) is quenched by the merocyanine, which is even more obvious if the data are corrected by the optical densities at the excitation wavelength. The latter result indicates an energy transfer process from the chromophore to the merocyanine that makes these switches interesting candidates for functional π-systems. The efficiency of this process increases from dyad **10a** over **10b** to **10c** due to the enhanced spectral overlap. In **10c**, however, the nile red cannot be excited selectively because the merocyanine absorbs in the same range. Dyad **10a** shows a small emission at ~650 nm probably due to an exciplex.

In conclusion we have demonstrated an improved and easily applicable synthetic methodology to assemble spiropyrans **4a**−**k**, **7a**−**f**, **8**, and **9** that are equipped with iodo, hydroxyl, azido, or ethinyl groups as building blocks for conjugation to functional π-systems or to biopolymers. Representatively, we have shown this for the preparation of spiropyran−chromophore conjugates as molecular dyads via the "click"-type cycloaddition. Due to their photoswitchable energy transfer properties the dyads **10a**−**c** represent promising photochromic compounds.

Experimental Section

1-(3-Hydroxypropyl)-2,3,3-trimethyl-3*H*-indolium Iodide (2). Freshly distilled **1** (1.5 mL, 9.34 mmol) was dissolved in $CHCl_3$ (17 mL) and degassed. 3-Iodo-1-propanol (1.00 g, 10.4 mmol) was added and the solution was refluxed for 24 h. The mixture was cooled to rt, the solvent was evaporated, and the oil was washed with petroleum ether and triturated with Et_2O to afford **2** as a purple solid (3.224 g, 99%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.01−7.91 (m, 1 H), 7.90−7.81 (m, 1 H), 7.67−7.57 (m, 2 H), 4.56 (t, 2 H, J = 6.9 Hz), 3.55 (t, 2 H, J = 5.5 Hz), 2.87 (s, 3 H), 2.11−1.97 (m, 2 H), 1.54 (s, 6 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 196.4, 141.7, 141.0, 129.2, 128.8, 123.4, 115.4, 57.8, 54.1, 45.7, 29.6, 21.8, 14.3, 5.4; MS (ESI, DCM/MeOH + 10 mmol/L NH_4Ac) m/z (%) 218.0 (100) [M^+].

(*S*)-3,4,10,10a-Tetrahydro-10,10,10a-trimethyl-2*H*-[1,3]oxazino[3,2-*a*]indole (3). **2** (3.09 g, 8.97 mmol) was suspended in degassed water (53 mL), finely ground KOH (1.23 g, 21.85 mmol) was added, and the mixture was stirred at rt for 2 h. CH_2Cl_2 (50 mL) was added and the mixture was stirred for 30 min. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 45 mL). The combined organic layers were washed with brine and water, then dried over Na_2SO_4. The solvent was evaporaterd. The residue was dried under vacuum and purified by flash chromatography on silica gel (petroleum ether:EtOAc 4:1 to 1:1) to afford **3** as colorless crystals (0.84 g, 43%). R_f 0.47 (hexane:EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (t, 1 H, J = 7.7 Hz, CH−C3), 7.08 (d, 1 H, J = 7.3 Hz, CH−C5), 6.81 (t, 1 H, J = 7.2 Hz, CH−C4), 6.59 (d, 1 H, J = 7.8 Hz, CH−C2), 4.08 (dt, 1 H, J = 2.6, 12.4 Hz, CH_2−C9), 3.72 (dd, 1 H, J = 5.2, 11.8 Hz, CH_2−C9), 3.66 (dd, 1 H, J = 4.6, 14.6 Hz, CH_2−C11), 3.54 (m, 1 H, CH_2−C11), 2.02−1.92 (m, 1 H, CH_2−C10), 1.56 (s, 3 H, CH_3−C14), 1.30 (s, 3 H, CH_3−C12), 1.20 (d, 1 H, J = 13.4 Hz, CH_2−C10), 1.07 (s, 3 H, CH_3−C13); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1 (C1), 139.2 (C6), 127.2 (C3), 122.0 (C5), 119.2 (C4), 108.6 (C2), 98.3 (C8), 61.0 (C9), 48.0 (C7), 39.1 (C11), 26.7 (C13), 21.7 (C10), 18.6 (C12), 13.0 (C14); HRMS (EI-MS) calcd for $C_{14}H_{19}NO$ [M^+] 217.1467, found 217.1472.

General Procedure for Synthesis of 4a−k. To a degassed solution of **3** (0.1 M for **4a** and **4h**, 0.06 M for **4b**−**g** and **4i**−**k**) in dry EtOH was added the salicylaldehyde (1.0 equiv). The mixture was sonicated at 35 kHz. EtOH was evaporated. The residue was taken up in CH_2Cl_2, washed with water, and dried over Na_2SO_4. The solvent was evaporated and dried under vacuum. The crude product was purified by flash chromatography on silica gel. For details for **4a**−**k** see the Supporting Information.

1-(3-Iodopropyl)-2,3,3-trimethylindolinium Iodide (5). Freshly distilled **1** (30 mL, 186.9 mmol) was dissolved in MeCN (40 mL) and degassed. Freshly distilled 1,3-diiodopropane (75 mL, 653 mmol) was added, and the reaction mixture was refluxed for 48 h. After cooling the solid was filtered off, washed with MeCN and $CHCl_3$ (2×), and dried in a vacuum to yield **5** as a pale gray-yellow solid (65.7 g, 77%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.02−7.94 (m, 1 H, arom., C8−H), 7.88−7.80 (m, 1 H, arom., C5−H), 7.69−7.59 (m, 2 H, arom., C6/7-H), 4.48 (t, 2 H, N−CH_2), 3.43 (t, 2 H, I−CH_2), 2.86 (s, 3 H, C2−Me), 2.41 (m, 2 H, CH_2−propyl), 1.55 (s, 6 H, C3−Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 197.3 (C_{quat}), 141.8 (C_{quat}), 141.1 (C_{quat}), 129.4 (C6), 128.9 (C7), 123.5 (C5), 115.2 (C8), 54.2 (C_{quat}), 48.4 (N−CH_2), 31.0 (CH_2−propyl), 22.0, 14.3

(C2−Me), 2.2 (I−CH_2); MS (ESI, DCM/MeOH + 10 mmol/L NH_4Ac) *m*/*z* (%) 327.8 (100) [M^+].

1-(3-Iodopropyl)-3,3-dimethyl-2-methyleneindoline (6). 5 (212 mg, 0.47 mmol) was suspended in degassed water (56 mL) and finely ground NaOH (559 mg, 14.0 mmol) was added. The mixture was heated at 80 °C for 15 min and cooled to rt, then Et_2O (60 mL) was added, with stirring for 1 h, and extracted with Et_2O and CH_2Cl_2 (2 × 20 mL). The organic layers were washed with water, combined, and dried over Na_2SO_4. The solvents were evaporated to yield **6** as a pale pink solid (139 mg, 91%). ^{1}H NMR (300 MHz) δ 7.18−7.08 (m, 2 H), 6.83−6.61 (m, 2 H), 3.93 (dd, 2 H, J = 1.9, 22.2 Hz), 3.63 (t, 2 H, J = 6.8 Hz), 3.23 (t, 2 H, J = 6.7 Hz), 2.21 (quint, 2 H, J = 6.8 Hz), 1.35 (s, 6 H); ^{13}C NMR (75 MHz) δ 161.5 (C_{quat}), 145.7 (C_{quat}), 137.5 (C_{quat}), 127.6 (+, CH), 122.0 (+, CH), 118.7 (+, CH), 105.3 (+, CH), 104.1 (+, CH_3), 87.5 (+, CH_3), 73.8 (−, CH_2), 44.3 (C_{quat}), 42.6 (−, CH_2), 30.1 (−, CH_2), 3.6 (−, CH_2); MS (EI, 70 eV) *m*/*z* (%) 184.0 (100) [$(M - HI - CH_3)^{+\bullet}$], 198.9 (42) [$(M - HI)^{+\bullet}$], 327.0 (9) [$M^{+\bullet}$].

General Procedure for Synthesis of 7a−f. Under degassed conditions freshly prepared **6** was dissolved in dry EtOH (0.1 M). Salicylaldehyde (1.0 equiv) was added, and the mixture was sonicated at 35 kHz. The solvent was evaporated, and the remaining residue was taken up in CH_2Cl_2, washed with water, and dried over $MgSO_4$. The solvent was evaporated. The raw product was dried under vacuum and purified with flash chromatography on silica gel. For details for **7a−f** see the Supporting Information.

1′-(3-Iodopropyl)-1′,3′-dihydro-3′.3′-dimethylspiro[3*H*]naphth-[2,1-*b*][1,4]oxazine (8). Freshly prepared **6** (348 mg, 1.06 mmol) was dissolved in dry EtOH (12 mL) and degassed. 1-Nitroso-2-naphthol (203 mg, 1.17 mmol) was added, and the mixture was sonicated for 2 h. The solvent was evaporated. The residue was dried under vacuum and purified by flash chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2:MeOH 200:1) to yield **8** as a yellow powder (126 mg, 25%). R_f 0.60 (CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, 1 H, J = 8.4 Hz), 7.78−7.72 (m, 2 H), 7.68 (d, 1 H, J = 8.9 Hz), 7.58 (ddd, 1 H, J = 1.1, 6.9, 8.3 Hz), 7.40 (ddd, 1 H, J = 1.2, 6.9, 8.1 Hz), 7.22 (dt, 1 H, J = 1.2, 7.7 Hz), 7.09 (dd, 1 H, J = 1.0, 7.3 Hz), 7.00 (d, 1 H, J = 8.9 Hz), 6.90 (dt, 1 H, J = 0.7, 7.4 Hz), 6.67 (d, 1 H, J = 7.8 Hz), 3.42−3.22 (m, 2 H), 3.20−3.09 (m, 2 H), 2.30−2.08 (m, 2 H), 1.35 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.0, 146.7, 143.7, 135.6, 130.8, 130.4, 129.3, 128.0, 127.8, 127.2, 124.2, 122.7, 121.8, 121.5, 119.8, 116.8, 106.9, 98.9, 52.1, 44.9, 32.5, 25.3, 21.0, 2.8; MS (ESI) *m*/*z* (%) 482.9 (100) [MH^+], 524.0 (16) [MH^+ + MeCN].

1′-(3-Azidopropyl)-1′,3′-dihydro-3′,3′-dimethyl-6-nitrospiro-[2*H*-1-benzopyran-2,2′[2*H*]-indole] (9). 7a (1.58 g, 3.31 mmol) was dissolved in dry DMF (62 mL), NaN_3 (877 mg, 13.49 mmol) was added, and the mixture was stirred in the dark at rt for 19 h. The solvent was evaporated. The residue was dried under vacuum and purified by flash chromatography on silica gel (CH_2Cl_2) to yield **9** as a golden foam (1.08 g, 83%). R_f 0.82 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.20 (dt, 1 H, J = 1.3, 7.7 Hz), 7.10 (dd, 1 H, J = 0.9, 7.3 Hz), 6.94 (d, 1 H, J = 10.3 Hz), 6.90 (dt, 1 H, J = 0.9, 7.5 Hz), 6.75 (d, 1 H, J = 8.4 Hz), 6.60 (d, 1 H, J = 7.8 Hz), 5.86 (d, 1 H, J = 10.4 Hz), 3.39−3.18 (m, 4 H), 2.01−1.90 (m, 1 H), 1.88−1.75 (m, 1 H), 1.29 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 146.8, 141.1, 136.0, 128.4, 127.8, 125.9, 122.8, 121.8, 121.6, 119.8, 118.4, 115.5, 106.7, 106.6, 52.6, 49.0, 40.8, 28.1, 25.9, 19.9; HRMS (PI-EI) calcd for $C_{21}H_{21}N_5O_3$ [$M^{+\bullet}$] 391.1644, found 391.1644.

Synthesis of Dyads 10a−c. To a solution of **9** (**10a**: 182 mg, 0.47 mmol; **10b**: 76 mg, 0.21 mmol; **10c**: 27 mg, 0.07 mmol) in 3:1 DMF:water (**10a**: 24 mL; **10b**: 20 mL, **10c**: 6 mL) were added 1-ethynylpyrene (105 mg, 0.46 mmol)/3-ethynylperylene (56 mg, 0.20 mmol)/ethynyl nile red (18 mg, 0.05 mmol), $CuSO_4 \cdot 5H_2O$ (**10a**: 17 mg, 0.07 mmol; **10b**: 8 mg, 0.03 mmol; **10c**: 2.6 mg, 0.01 mmol), tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (**10a**: 12 mg, 0.02 mmol; **10b**: 7 mg, 0.01 mmol; **10c**: 2.0 mg, 0.01 mmol), and (+)-sodium L-ascorbate (**10a**: 27 mg, 0.14 mmol; **10b**: 14 mg, 0.07 mmol; **10c**: 4.2 mg, 0.02 mmol). The mixture was stirred at rt (∼24 h), diluted with EtOAc, and washed with brine and water. The aqueous phase was again extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH **10a**: 200:1 to 100:1; **10b**: 1000:1 to 20:1; **10c**: 300:1 to 70:1) to afford **10a** as a pale green foam (262 mg, 91%), **10b** as a yellow solid (123 mg, 91%), or **10c** as a pink solid (32.3 mg, 84%). For details for **10a−c** see the Supporting Information.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the University of Regensburg.

Supporting Information Available: Experimental procedures, data and images of ^{1}H/^{13}C NMR spectra, MS analysis for **2**, **3**, **4a−k**, **5**, **6**, **7a−f**, **8**, **9**, **10a−c**, and crystallographic data of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.