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Synthesis of Photochromic Compounds for Aqueous Solutions and Focusable Light

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Photochromic compounds with improved performance in pure water have been prepared and characterized. They possess an asymmetrical and extended conjugation system with a 1,2-bis(3-thienyl)perfluorocyclopentene core, additional thiophene rings connected with sulfonic acid residues, as well as terminal pyrid-4-yl and 4-alkoxyphenyl groups. A multistep synthetic route to a key compound with an amino group required for further derivatization has been developed. The complete photocyclization reaction of the initial "open ring" compound (with absorption maximum at 340 nm in MeOH or water) can be performed with a diode laser in pure water or aqueous buffer solutions (without added organic solvents) under irradiation at 366–375 nm, and the reverse ring-opening reaction of the colored "closed ring" compound (λ_{max} = 628 or 624 nm in MeOH or water) takes place under irradiation with visible green or red light (>500 nm). Building block **57**, with a secondary amino group, can further be used in the synthesis of practically important, reversibly switchable, fluorescent compounds in which the fluorescent dye (donor) is attached to a photochromic unit (acceptor), and the resonant energy transfer from a donor to the colored form of an acceptor provides a reversible quenching of the fluorescence signal in aqueous solutions.

Introduction

Photochromic compounds can be reversibly converted by light between two states with different spectroscopic properties.[1] Moreover, various secondary functions of photochromic compounds and their adducts (e.g., fluorescence quantum yields, dipole moments, oxidation potentials, acidity constants, etc.) can be switched by light. A reversible modulation of the fluorescence signal can be achieved,[2] for example, if the photochromic unit is attached to a fluorescent dye, and a photochromic resonant energy transfer (pcRET) takes place.[3] For efficient energy transfer, the emission band of the fluorescence dye (RET donor) must overlap with an absorption band of the colored state of the photochromic unit (RET acceptor). It was proposed that reversible switching of fluorescent markers between the fluorescent and non-fluorescent state may be used for the acquisition of optical images with diffraction-unlimited resolution.[4] For that, the fluorescence signal of the labeled object must be switched on and off reversibly by converting the photochromic unit from a colorless into a colored form.[5] The optical resolution can be improved, provided that hundreds or thousands of such cycles can be performed without considerable loss of contrast (caused by photobleaching). An advantage of the fluorescent photochromic compounds is that the light intensity required for switching are much lower than those commonly used in other far-field nanoscopy techniques[6] (e.g., stimulated emission depletion[7] or ground state depletion with individual molecular return[8]). Therefore, the drastic reduction in the applied light intensities would be highly beneficial to avoid photodamage to live cells and other biological objects.

Modern microscopy techniques demand photochromic compounds that can be reversibly switched between colorless and colored states by irradiation with focused light. The technique also requires the application of high-quality optics that are available for visible and near-UV light. However, aberration-corrected lenses with large numerical apertures (1.35–1.45) exist only for wavelengths greater than 360 nm. Thus, the compact and relatively inexpensive, commercially available diode lasers, which typically operate at 375 nm, are convenient and provide one of the shortest wavelengths available for optical switching in life sciences.

Among the different families of photochromic compounds, diarylethenes that contain a perfluorocyclopentene unit, are regarded as the most promising, particularly for photoswitching applications in optical nanoscopy, pcRET, and data storage. Key features of these compounds are bistability (absence of thermal reactions competing with photochromic transformations) and a large fatigue resistance (photostability). Despite the large number of known diarylethenes,[9] only a few can be switched at wavelengths

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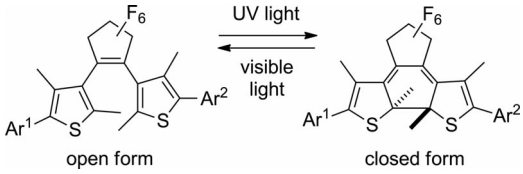
longer than 360 nm. In 2006, we described the synthesis and properties of photoswitchable compounds with a high degree of fluorescence modulation (up to 96% in methanol or ethanol) under irradiation with light of 375 nm (off-switching) and 660 nm (on-switching).[10] One of these photochromic fluorescent compounds was incorporated into 30 nm silica gel beads, and it was shown that the optical resolution (along one axis) could be significantly improved by switching "on" and "off" the fluorescence signal of single nanoparticles for 30 full cycles (two beads at a distance of 230 nm were resolved).[11] This study showed that the bleaching of the photochromic unit allowed only about 100 cycles to be performed without considerable photofatigue effects, although the 1,2-bis(3-thienyl)perfluorocyclopentenes (Scheme 1) used in this work belong to one of the most photostable classes of photochromic compounds.[9a] An important limiting factor is that we could not perform even one complete switching cycle in water with these lipophilic diarylethenes, even when they were decorated with a long oligo-ethylene glycol chain to provide solubility in aqueous media.[12]



Scheme 1. Photochromism of 1,2-bis(thiophen-3-yl)cyclopentenes.

However, good performance in water or aqueous buffer is ultimately required for molecular markers and labels that are suitable for use in life sciences. Therefore, the goal of the present work was the synthesis and characterization of hydrophilic photochromic compounds with good performance in pure water (or aqueous buffer) in the course of irradiation with focusable light at wavelengths longer than 360 nm.

Results and Discussion

1. Background: Photochromic Diarylperfluorocyclopentenes with Improved Solubility in Aqueous Media

Most molecular probes for use in biology and life sciences are applied in water or aqueous buffers (as free substances or bioconjugates). Even a low content of organic solvent may cause protein denaturation or cell death. It was anticipated that the poor performance of photochromic compounds in aqueous solutions may be improved by synthesizing their hydrophilic derivatives. 1,2-Bis(hetaryl)perfluorocyclopentenes are excellent photochromic compounds that can be switched many times, and their colorless and colored forms are chemically and thermally stable.[9a] In 1997, Irie's group reported the preparation of water-soluble 1,2-bis(2-methyl-1-benzo[*b*]thiophene-3-yl)perfluorocyclopentenes with two sulfonic acid groups attached to the benzene rings.[13] In aqueous media, this compound was found to be photochromic; after irradiation at 313 nm, the initial colorless solution turned red, and new absorption bands appeared at 358 and 529 nm; the reverse reaction was driven by irradiation with visible light (>480 nm).

A series of reports described photochromic diarylethenes with amphiphilic side chains. The photochromic core was always based on 1,2-bis(2-methyl-5-phenylthiophen-3-yl)-perfluorocyclopentene. In the first study,[14] diarylethenes with hexa(ethylene glycol) units attached to phenyl rings were prepared and their photochromic properties and self-assembling behavior were studied. These compounds showed excellent photochromic performance in organic solvents and even in aqueous media, in which levels of photoconversion under irradiation with 313 nm light reached 86–91%. The absorption maxima of the colorless open-ring isomers in aqueous solution were observed at 289–294 nm, and the absorption maxima of the closed-ring isomers were found to be at 573–583 nm. However, due to hydrophobic interactions, these molecules were found to be self-associated (nanodomains of around 100 nm in size in water at room temperature), and their solutions became cloudy upon heating. In general, self-association is undesirable for fluorescent probes because this may lead to fluorescence quenching after aggregation. In 2008, the same group reported a similar bis-hexa(ethylene glycol)diarylethene hybrid structure with an amide group near the aromatic core.[15] The colorless open form of this compound absorbed at around 310 nm, and the absorption maximum of the closed-ring isomer was located at 598 nm in water. Recently, a number of diarylethene derivatives with various oligo(ethylene glycol) side chains have been prepared.[16] The size of the aggregates and the self-assembling behavior depended on the lengths of the amphiphilic side chains. Compounds with six hexa(ethylene glycol) side chains and enhanced solubility were shown to give molecularly dispersed solutions in water, whereas the solubility of compounds with shorter side chains in water was very poor. However, none of these symmetric photochromic compounds possess an additional functional group necessary for attaching them to fluorescent dyes. More critically, their absorbance at 375 nm is too low, and thus cannot be used for effective switching.

In 2007, Irie and co-workers attempted to use the new perfluorocyclopentene derivative as a fluorescence switching agent for the labeling of proteins. They synthesized a derivative of 1,2-bis(2,4-dimethyl-5-phenylthiophen-3-yl)-perfluorocyclopentene attached to fluoresceine as a fluorescent dye.[17] Reversible fluorescence switching was observed along with the photochromic reaction. Irradiation at 365 nm produced the closed-ring isomer with absorption at 580 nm, and the fluorescence intensity decreased. After irradiation with visible light ($\lambda > 550$ nm), both absorption and fluorescence spectra returned to their original state. Modulation of the fluorescence was found to be 60% due to the moderate conversion between the open and closed forms in the photostationary state (PSS). After deprotection of the carboxy group attached to phenyl ring, the fluorescent photochromic compound was decorated with a suc-

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cinimidyl ester group and attached to a protein. The absorption and fluorescence spectral changes of the labeled protein were reported for the solution in PBS buffer containing 30% EtOH. However, because the high content of ethanol as an organic solvent is inappropriate for life science applications, hydrophilic photochromic compounds with considerable absorption in the near-UV region and with the ability to switch reliably in pure water or buffer solutions need to be developed.

2. Attachment of the Sulfonic Acid Residues to the Lipophilic Photochromic Units with Extended Conjugated Systems

2.1. Attempted Modifications of the Thiophene Rings Attached to the Perfluorocyclopentane Core

In 2006, we described the synthesis and properties of apolar photochromic compounds that undergo ring-closing and ring-opening reactions under irradiation with 375 and 660 nm light.[10] According to HPLC analysis, the photoconversion in ethanol or methanol was nearly complete. We planned to increase the water-solubility of this photochromic unit (Figure 1) by introducing sulfonic acid groups. Hydrophilic residues (with linkers) can be connected to the carbon atoms (C-4) adjacent to the perfluorocyclopentene fragment (priority 1 modification), or they may be attached to the central 3,4-unsubstituted thiophenes (priority 2 modification) (Figure 1). After deprotection, the amino group was expected to react with a fluorescent dye. The whole synthetic scheme was designed in such a way that an additional *O*-protected 3-hydroxypropyl residue (R) could be attached to the amino group. Later, this moiety could be used to link the whole molecule with an object, provided that the deprotected alcohol could be converted into the *O*-succinimydyl carbonate.

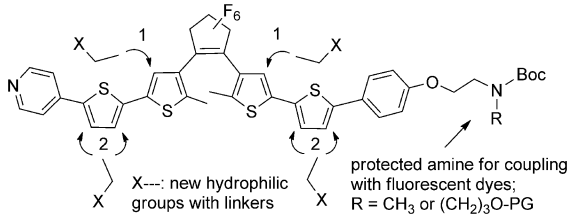
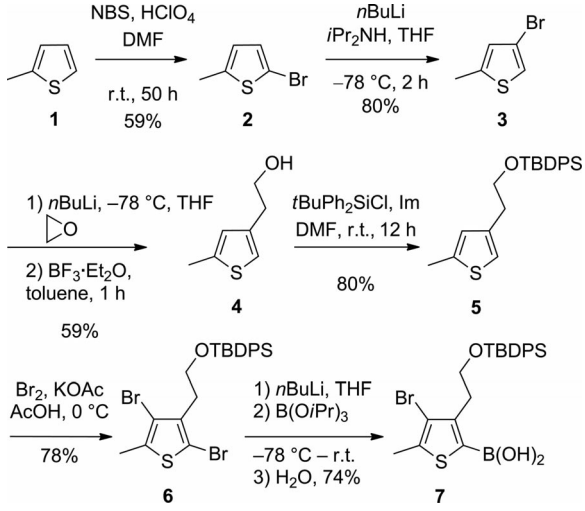


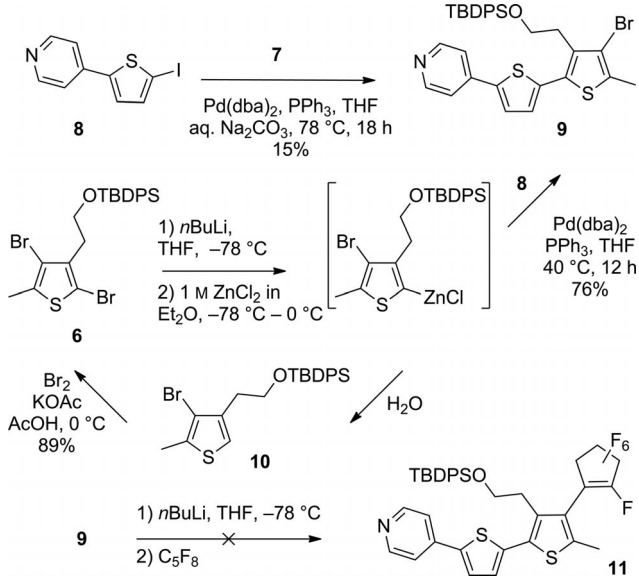
Figure 1. Photochromic compounds[10] for decoration with hydrophilic groups according to priority 1 and priority 2 modifications.

2-Methylthiophene (**1**) was used as the starting material to implement the priority 1 modifications. It was brominated with *N*-bromosuccinimide (NBS) in the presence of $HClO_4$,[18] and then bromide **2** was smoothly transformed into 4-bromo-2-methylthiophene (**3**) in the course of a "halogen dance" (Scheme 2). The latter compound was subjected to bromine–lithium exchange, and the lithio-derivative was treated with oxirane.[19] The hydroxy group in compound **4** was protected with a *tert*-butyldiphenylsilyl (TBDPS) residue, which was stable to hydrolysis during the subsequent synthetic procedures. The thiophene **5** was brominated to afford the colorless crystalline bromide **6**, which was transformed into boronic acid **7** in good yield.



Scheme 2. Synthesis of the boronic acid **7** and its precursor **6** with a protected hydroxy group.

The Suzuki coupling of iodide **8** with boronic acid **7** gave compound **9** in low yield. To reduce the number of steps, the coupling reaction was performed with the zinc-derivative of compound **6** (Scheme 3). Towards this end, selective lithiation of dibromide **6** followed by addition of $ZnCl_2$ was performed, and the reaction mixture was added into the flask containing iodide **8** and a palladium catalyst. The coupling product – the "left hand" precursor **9** – was isolated in good yield. The dehalogenated derivative **10**, which was obtained as a side-product by hydrolysis of the zinc derivative, was also isolated and successively rebrominated to substrate **6**. Unfortunately, the required heptafluorocyclopentene derivative **11** could not be obtained from iodide **9** and



Scheme 3. Synthesis of the "left hand" precursor **8** of the photochromic unit.

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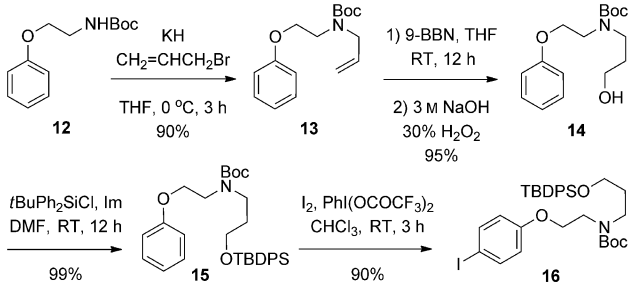
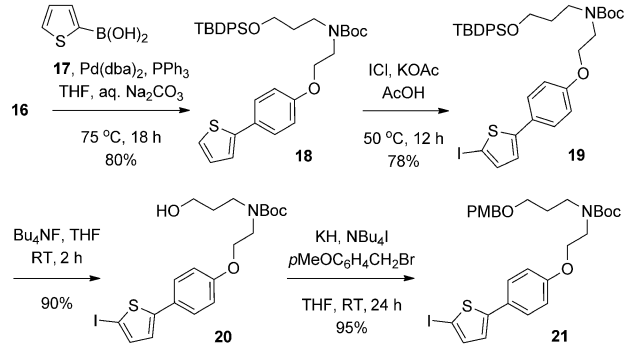
perfluorocyclopentene (probably due to the cleavage or migration of the TBDPS protecting group).

Synthesis of the precursor of the "right hand" part of the photochromic unit is depicted in Scheme 4. The phenoxyethylamine derivative **12** was alkylated with allyl bromide, and the terminal double bond of **13** was subjected to hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidation.[20] Alcohol **14** was protected with a TBDPS group, and compound **15** was iodinated with bis(trifluoroacetoxy)iodobenzene. Iodide **16** was coupled with thiophene-2-boronic acid (**17**), and compound **18** was further iodinated with ICl in acetic acid to afford **19** in good yield (Scheme 5). At this stage, the hydroxy function was deblocked in order to change the protecting group and purify the solid intermediate substance.



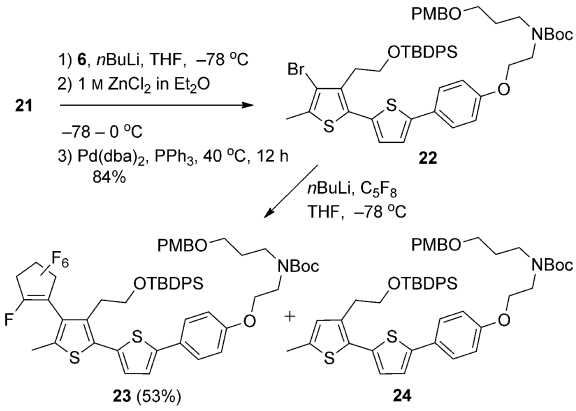
Scheme 4. Generating the diprotected aryl iodide **16**.



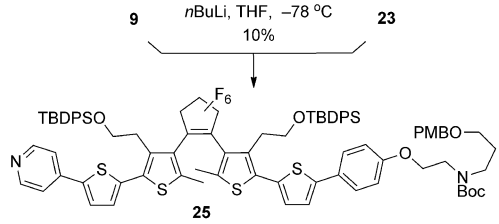
Scheme 5. Generating the "right hand" precursor of the photochromic unit.

The hydroxy group in compound **20** was protected with *p*-methoxybenzyl chloride, and biaryl **21** was coupled with the Zn derivative of **6** in the presence of the palladium catalyst [$Pd(dba)_2$]. The triaryl compound **22** was isolated in good yield (Scheme 6). Unfortunately, after lithiation of **22** and its interaction with an excess of perfluorocyclopentene, the required heptafluorocyclopentene **23** was obtained as an inseparable mixture with the dehalogenated derivative **24**. The reaction of the lithiated derivative of **9** with this mixture gave the required photochromic compound **25** in low yield (Scheme 7).

Deprotection of the hydroxy groups was expected to help to separate the corresponding alcohols and obtain compound **26** (Scheme 8). Unfortunately, deprotection was accompanied by the loss of one or three fluorine atoms and formation of a mixture of compounds **27**–**29**. Under basic

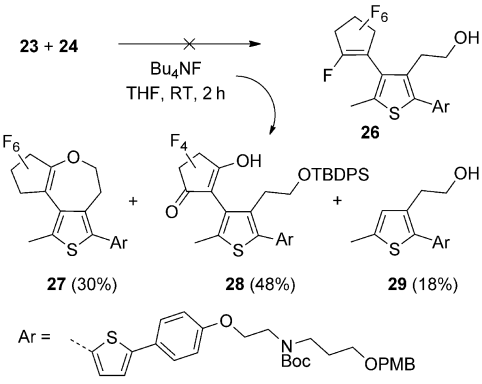


Scheme 6. Generating the heptafluorocyclopentene derivative **23** – the "right hand" precursor of the photochromic compound.



Scheme 7. Photochromic compound **25** with protected hydroxy groups.

conditions, a fluorine atom was substituted by the adjacent hydroxy group, and the seven-membered ring compound **27** was formed.



Scheme 8. Deprotection of the hydroxy groups near the perfluorocyclopentane ring under basic conditions.

Simultaneously, due to the presence of water in Bu_4NF, diketone **28** was produced. Clearly, compounds **27** and **28** were formed during the base-catalyzed nucleophilic addition of ROH (R = alkyl, H) to the extremely electron-poor C=C bond, followed by elimination of one or several HF molecules (alcohol **29** was formed from the silylated precursor **24**).

When the mixture of compounds **23** and **24** was introduced into the reaction with the lithiated bromide **30** (obtained from dibromide **6** through substitution of the α-bromine atom with a trimethylsilyl residue), the expected pho-

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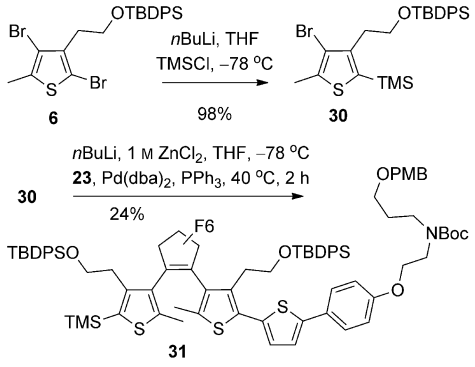
tochromic adduct **31** was isolated, albeit in low yield (Scheme 9). These synthetic difficulties forced us to embark on the priority 2 modifications.

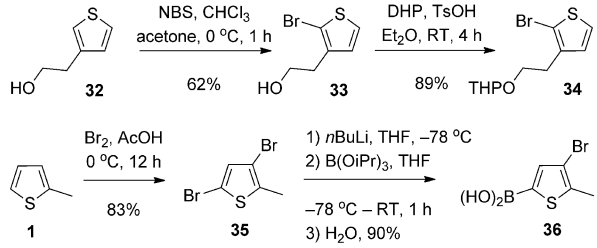


Scheme 9. Synthesis of the model photochromic compound **31**.

2.2. Attachment of the Sulfonic Acid Residues to the "Middle" Thiophene Rings

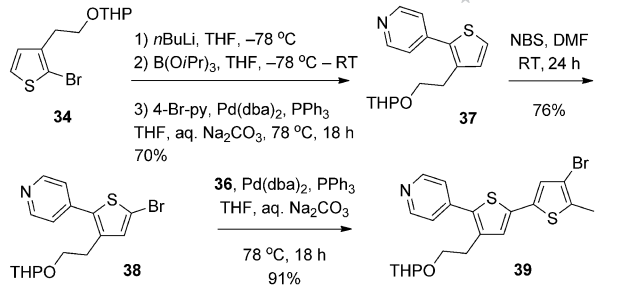
Modifications of the second type (Figure 1) were expected to be free from the drawbacks mentioned above. The hydroxy groups in this approach are far from the central fluorinated part of the photochromic unit.

As a starting compound with an additional functional group, we used 3-(2-hydroxyethyl)thiophene (**32**), which was selectively brominated with NBS in the 2-position of the thiophene ring. The hydroxy group in compound **33**[21a,21b] was then protected with a tetrahydropyranyl residue (Scheme 10). The reverse order of reactions (protection of hydroxy groups followed by bromination according to known procedures[21c]) led to lower overall yields of compound **34**. 2-Methylthiophene (**1**) was used as a second building block, which, after bromination in acetic acid and monolithiation followed by addition of $B(OiPr)_3$, afforded boronic acid **36**[21d,21e] in good yield.



Scheme 10. Thiophene bromides **34** and **36** as small building blocks.

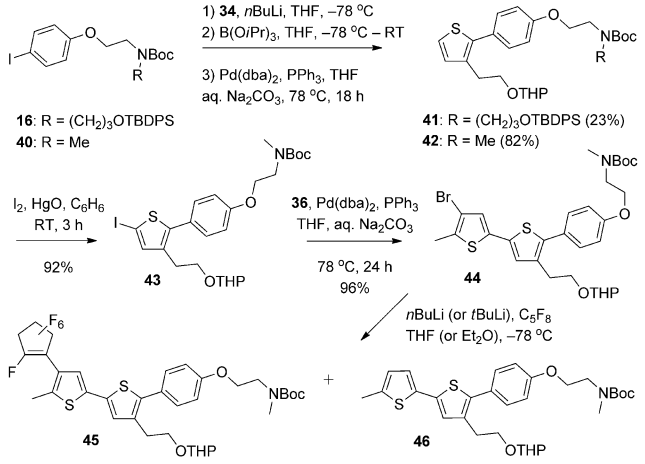
Bromothiophene **34** was also transformed into the corresponding boronic acid and used in the Suzuki coupling with 4-bromopyridine (Scheme 11). Attempted iodination of the isolated compound **37** with iodine in the presence of either periodic acid in ethanol or bis(trifluoroacetoxy)iodobenzene (in $CHCl_3$ or 80% aq. acetic acid), was unsuccessful and gave either only the starting material or the deprotected compound, respectively.



Scheme 11. The"left hand" building block **39** of the photochromic unit.

The reaction of **37** with *n*BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine followed by addition of CBr_4[22] did not lead to formation of the desired compound **38**. Fortunately, compound **37** could be brominated with NBS, and bromide **38** was coupled with thiopheneboronic acid **36**. The pure building block **39** was isolated by chromatography on silica gel.

Initially, aryl iodide **16** was coupled with bromothiophene **34**, but the yield of product **41** was low. Therefore, aryl iodide **40** was first transformed into compound **42** by a Suzuki coupling with the boronic acid obtained from bromothiophene **34** (Scheme 12). Compound **42** was then iodinated with I_2 and HgO in benzene, and iodide **43** was isolated in high yield. The latter compound was coupled with 3-bromo-2-methylthiophene-5-boronic acid (**36**) to give the "right hand" precursor **44** in very good yield.



Scheme 12. "Right hand" precursor **44** of the photochromic unit and the products **45** and **46** isolated after its reaction with perfluorocyclopentene.

Both the "right" and the "left hand" precursors **44** and **39** were subjected to halogen–lithium exchange followed by treatment with an excess of perfluorocyclopentene. In the first case, heptafluorocyclopentene derivative **45** could not be separated from dehalogenated compound **46** (Scheme 12). In the second case, the yield of the required heptafluorocyclopentene **47** was found to be lower due to a side reaction.

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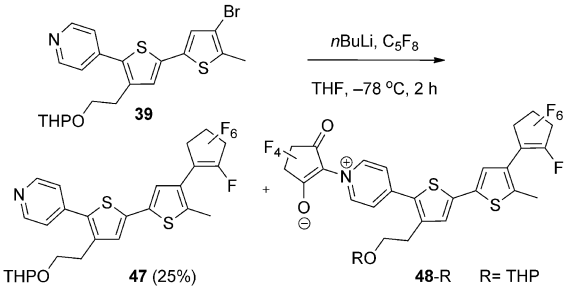
A very interesting compound with a betaine structure (**48**-THP) was isolated from the reaction of lithiated compound **39** with perfluorocyclopentene (Scheme 13). The highly fluorescent betaine **48**-THP absorbs at 440 nm (chloroform) and emits with a maximum at 502 nm (excitation at 420 nm). The emission band is broad due to a shoulder at 530 nm, so that the "effective" Stokes shift is more than 60 nm. The fluorescence quantum yield was found to be 0.51 (in chloroform). The optical spectra of betaine **48**-THP were reminiscent of Lucifer Yellow or Coumarine 153.[23] A combination of a large Stokes shift with relatively high emission efficiency is a very interesting feature. Unfortunately, in polar solvents (e.g., alcohols), betaine **48** emits poorly.



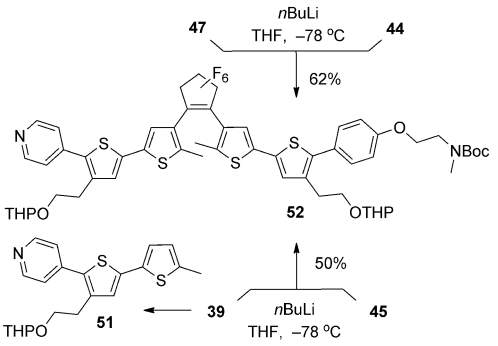
Scheme 13. Synthesis of the heptafluorocyclopentene derivative **47** and betaine **48**.

The formation of betaine **48** was not observed at –78 °C. However, when this reaction was quenched at this temperature, the same by-product was formed and detected during the work-up or isolation procedures (unless the excess of perfluorocyclopentene was removed completely as early as possible). Moreover, the isolated compound **47** was found to be unstable at temperatures higher than 0 °C. Therefore, **47** was either used immediately after isolation or kept under argon at –18 °C. The formation of the side product **48**, with a betaine structure, may be easily explained by nucleophilic addition of the pyridine residue to the highly reactive double bond in perfluorocyclopentene, followed by the step-wise hydrolytic substitution of the fluorine atoms at the activated positions.[24]

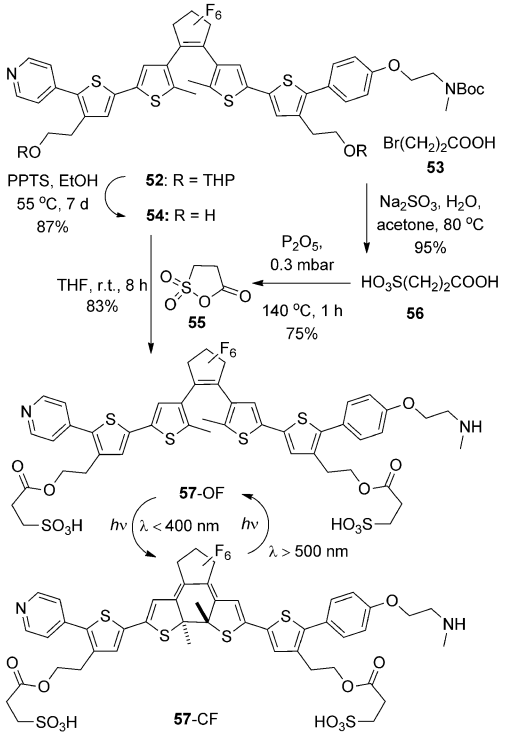
In both reactions generating heptafluorocyclopentenes **45** (Scheme 12) and **47** (Scheme 13), symmetric photochromic compounds **49** and **50** were also isolated as by-products (for structures, see Figure S1 in the Supporting Information).

Coupling of heptafluorocyclopentene **47** with the lithiated derivative of compound **44** gave the required photochromic compound **52** in good yield (Scheme 14), whereas the reaction of heptafluorocyclopentene **45** with bromide **39** (after its lithiation) resulted in the formation of a mixture of compound **52** and debrominated derivative **51** with very similar R_f values.

Initially, we tried to insert sulfonic acid residues through nucleophilic substitution of bromine atoms, which we expected to introduce through the reaction of the THP-protecting groups in compound **52** with bromine and PPh_3. Unfortunately, we were unable to isolate the required dibromide from the reaction mixture. Therefore, another synthetic approach was used. The THP-protecting groups in photochromic compound **52** were cleaved off under mild conditions using pyridinium *p*-toluenesulfonate (PPTS) in ethanol. The liberated hydroxy groups in compound **54** were then acylated with β-sulfopropionic anhydride (**55**; Scheme 15). The latter compound was obtained by dehydration of 3-sulfopropionic acid (**56**) with phosphorus pentoxide.[25] 3-Sulfopropionic acid was prepared from 3-bromopropionic acid (**53**) by stirring with Na_2SO_3 in aqueous acetone. The Boc-protecting group in compound **54** was also removed at this step, and the target water-soluble photochromic compound **57** was isolated in good yield.



Scheme 14. Synthesis of the asymmetric photochromic compound **52** with protected hydroxy groups.



Scheme 15. Synthesis of the target photochromic and water-soluble building block **57** with a free secondary amino group.

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3. Properties of the Water-Soluble Photochromic Diarylethene Prepared in This Study

The water-soluble photochromic compound **57** may be switched to the colored, closed form by irradiation with UV or violet light (365–375 nm; Figure 2 and Table 1). The colorless, open-ring isomer of compound **57** has an absorption maximum at 340 nm in MeOH ($\varepsilon = 4.1 \times 10^4$ $M^{-1}cm^{-1}$) and in water ($\varepsilon = 2.2 \times 10^4$ $M^{-1}cm^{-1}$). A secondary peak is observed at 258 nm ($\varepsilon = 2.6 \times 10^4$ and 1.7×10^4 $M^{-1}cm^{-1}$ in MeOH and water, respectively). Irradiation with 366 or 375 nm light transforms the initial substance into the blue-colored closed form with a broad absorption band around 626 nm in both methanol and water ($\varepsilon = 1.9 \times 10^4$ and 1.4×10^4 $M^{-1}cm^{-1}$ in MeOH and water, respectively). Irradiation with green or red light (>500 nm) restores the initial absorption spectrum of the photochromic compound (Figure 2). Several isosbestic points are observed in Figure 2 (A–C), which represent switching of compound **57** in both directions with UV and visible light. The presence of isosbestic points indicates the reversibility of the photochromic reaction involving two isomers, and that the photochemical transformations are not accompanied by the formation of observable amounts of by-products with (photo)chemically modified chromophores.

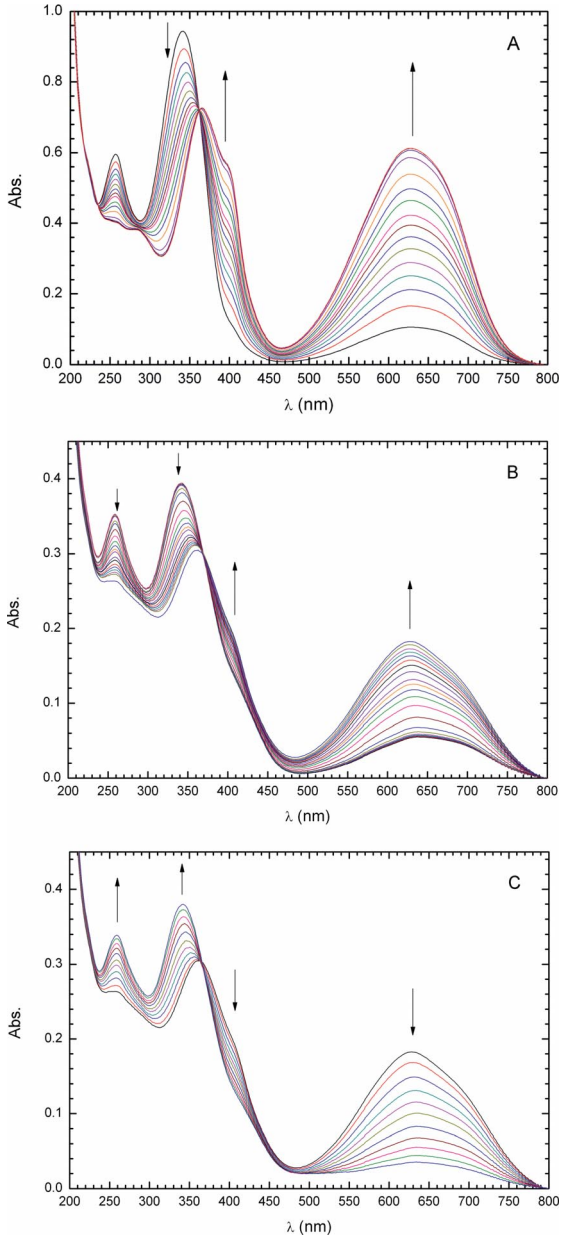

Figure 2. Absorption spectra of compound **57** undergoing photoconversion between the open- and closed-ring isomers upon irradiation at 366 nm in MeOH (A) and in water (B). The reverse reaction upon irradiation at 550 nm in water (C). The arrows indicate changes upon irridiation with UV (A and B) and green (or red) light (C).

Table 1. Absorption maxima of compound **57** in methanol and water (for spectra, see Figure S5 in the Supporting Information).

Isomer[a]	Solvent	λ [nm]	log ε[b]	λ [nm]	log ε[b]
57-OF	MeOH	257	4.41	340	4.61
	H_2O	258	4.23	340	4.34
57-CF	MeOH	366	4.34	628	4.28
	H_2O	367	4.26	624	4.15

[a] OF: "open form"; CF: "closed form". [b] $M^{-1}cm^{-1}$.

Initially, solutions of compound **57** in methanol and water were blue (Figure 2, A and B), indicating the presence of the "closed" isomer.

Interestingly, the amount of colored "closed" form in the isolated compound **57** is higher (ca. 20%, according to HPLC) than that found for the structurally similar compound with additional methyl groups in positions 4 and 4′ of the thiophene fragments attached to the central perfluorocyclopentene ring.[10] The absence of these methyl groups (situated in close proximity to the perfluorocyclopentene cycle) in compound **57**, eliminates the repulsion forces in the closed isomer and therefore stabilizes it.[26]

By performing the ring-opening reaction with green or red light, the concentration of the colored, closed form may be reduced, compared with the initial content (compare Figure 2, C and B). In this case (Figure 2, C), we stopped the experiment after irradiation for eight hours (ca. 20 mW/cm^2 at 550 nm). Full conversion into the open-ring isomer was achieved in both aqueous and methanolic solutions within a few minutes by using a halogen lamp (500 W) with a red filter. Irradiation with larger intensities is advantageous, because it allows compound **57** to be switched faster. In future applications, the irradiation will be performed with laser sources using focused light instead of a collimated mercury lamp, as in the present experiments.

The data on the kinetics of the ring-closing reaction upon irradiation with UV light in methanol and water are given in Figure 3. These experiments were conducted under identical irradiation conditions (the only difference was the concentration of the dye: 40 μM in MeOH and 24 μM in water). It is interesting that the cyclization of the photochromic compound **57** proceeds in these solvents with very different rates. In methanol, full conversion into the closed form was achieved in 5 min, whereas in water the absorp-

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tion signal at 627 nm was still increasing after irradiation for 1.5 h. We monitored the course of the photochemical transformations by HPLC, which showed that the full conversions into the ring-closed and ring-open isomers can be achieved (see Exp. Sect. for HPLC conditions, which provided the separation of the peaks of the open- and closed-ring isomers).

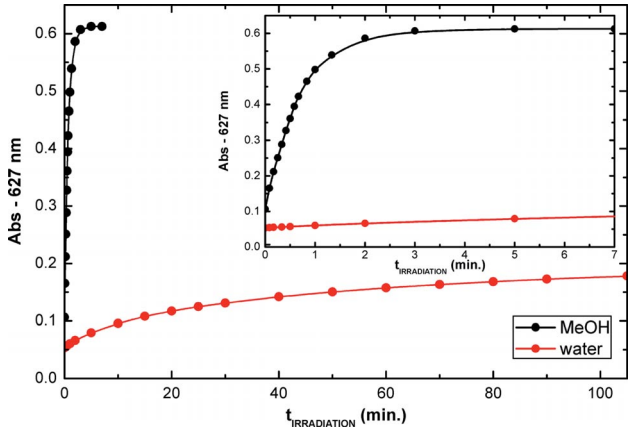

Figure 3. Kinetics of the cyclization reaction of compound **57** in MeOH (black dots) and water (red dots) under irradiation with 366 nm light.

The calculated quantum yields for the photocyclization reaction are 0.59 and 0.028 in methanol and water, respectively.

Irradiation of the sample with monochromatic light of 550 nm allowed the quantum yield of the reverse ring-opening reaction to be calculated. Similar values, within experimental error, of 5.8×10^{-4} and 2.0×10^{-4} in methanol and water, respectively, were obtained. A probable explanation for the differences observed in the reaction quantum yields can be drawn: the highly ordered structure of water, with its long-range network of hydrogen bonds, is responsible for the slow reaction rate of the cyclization reaction. The "open" form of compound **57** has much more degrees of rotational freedom and is less polar that the "closed" isomer. The direct π-conjugation between the electron-acceptor (pyridine ring) and electron-donor groups (phenol residue) is possible only in the closed-ring isomer with considerable charge separation. Thus, the enthalpy of activation (from the excited state) in water is expected to be lower than that in methanol ($\Delta\Delta H^{\neq} < 0$). However, changes in the polarity during the transition from the initial substance (in the excited state) to the ring-closed product may require significant restructuring of the whole shell of hydrogen bonds and dipoles of water molecules around the reacting species. Transition to the final state, with a lower degree of rotational freedom and highly ordered network of hydrogen bonds and solvent dipoles, is equivalent to the negative change in the activation entropy ($\Delta\Delta S^{\neq} < 0$, reference reaction from the excited state in methanol), and may result in the unfavorable change in the free activation energy in water ($\Delta\Delta G^{\neq} = \Delta\Delta H - T\Delta\Delta S^{\neq} > 0$); even if the enthalpy of activation in water is lower than in methanol ($\Delta\Delta H^{\neq} < 0$). The reverse reaction was found to be almost independent of the solvent (MeOH or water), or at least affected to a far lesser extent.

Conclusion and Outlook

The new, water-soluble photochromic compound **57** introduced here can be reversibly switched in aqueous solutions and in methanol with focusable light of wavelengths longer than 360 nm. Compound **57** was obtained during a convergent synthesis in which the longest reaction sequence consisted of only nine steps. All steps (except for the transformation **39**→**47**, which provided only 25% yield) afforded good yields, so that the total yield was about 3%. The target compound contains a secondary amino group that may be used to attach fluorescent compounds or intermediate linkers with a truncation point.[11] Further syntheses with building block **57** may provide fluorescent photochromic compounds, and it will be interesting to study their switching behavior in aqueous solutions.

Experimental Section

General: Anhydrous THF and diethyl ether were distilled from sodium benzophenone ketyl. Reactions were carried out under argon with magnetic stirring in Schlenk flasks equipped with septa or reflux condensers with bubble-counters using a standard manifold with vacuum and argon lines. Elemental analyses were carried out in Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie. Routine NMR spectra were recorded with a Varian MERCURY-300 spectrometer operating at 300.5 (^{1}H), 75.5 (^{13}C and APT), and 282.4 (^{19}F) MHz. ^{1}H and ^{13}C NMR spectra were also recorded with Varian INOVA 600 (600 MHz) and Varian INOVA 500 (125.7 MHz) instruments, respectively. All NMR spectra were referenced to tetramethylsilane as an internal standard (δ = 0 ppm) using the signals of the residual protons of $CDCl_3$ (δ = 7.26 ppm) or [D_6]DMSO (δ = 2.50 ppm). Multiplicities of signals are described as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, quint = quintet, m = multiplet. Low-resolution mass spectra (ESI) were obtained with LCQ and ESI-TOF mass-spectrometers [MICROTOF (focus), Fa. Bruker]. A MICROTOF spectrometer equipped with an ESI ion source Apollo and direct injector with LC autosampler Agilent RR 1200 was used to obtain high-resolution mass spectra (ESI-HRMS). ESI-HRMS were also obtained with an APEX IV spectrometer (Bruker). The HPLC system (Knauer) included a Smartline pump 1000 (2x), UV detector 2500, column thermostat 4000 (25 °C), mixing chamber, injection valve with 20 μL loop for the analytical column; 6-port/3-channel switching valve; analytical column [Eurospher-100 C18; 5 μm; 250 × 4 mm; 1.2 mL/min; solvent A: H_2O (HPLC grade) + 0.1% v/v TFA; solvent B: MeCN + 0.1% v/v TFA; detection at 254 nm and 25 °C (if not stated otherwise)]. UV/Vis absorption spectra were recorded with a Varian Cary 4000 UV/Vis spectrophotometer, and fluorescence spectra with a Varian Cary Eclipse fluorescence spectrophotometer. Irradiation experiments and the determination of quantum efficiencies of the isomerization reactions were previously reported.[27] The purities of the compounds were monitored by TLC on MERCK ready-to-use plates with silica gel 60 (F_{254}). Column chromatography: Merck silica gel, grade 60, 0.04–0.063 mm.

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4-{3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]thiophen-2-yl}pyridine (37): To a solution of **34** (8.73 g, 30.0 mmol) in anhydrous THF (150 mL), *n*BuLi (2.5 M in hexane, 13.2 mL, 33.0 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Then $B(OiPr)_3$ (8.46 g, 45.0 mmol) was added, and the mixture was stirred for 1 h at –78 °C and then for 2 h at room temperature. Water (2 mL) was added, followed by 4-bromopyridine hydrochloride (7.0 g, 36 mmol), Ph_3P (315 mg, 1.2 mmol), $[Pd(dba)_2]$ (173 mg, 0.30 mmol), and 20% aq. Na_2CO_3 (150 mL), and the mixture was heated under argon at 78 °C (bath temp.) for 18 h in a flask equipped with a reflux condenser and a bubble counter. The reaction mixture was diluted with EtOAc (100 mL) and the organic layer was separated, washed with brine (50 mL), dried, and evaporated under reduced pressure. The title compound was isolated by chromatography (200 g of SiO_2; hexane/EtOAc, 4:1→1:1) to yield **37** (6.1 g, 70%) as a colorless oil. R_f = 0.14 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.85 (m, 6 H, 3×CH_2, 3/4/5-H), 3.10 (t, J = 6.9 Hz, 2 H, CH_2), 3.41–3.49 (m, 1 H, CHH-6), 3.65 (dt, J = 6.9, 9.7 Hz, 1 H, CHHO), 3.67–3.76 (m, 1 H, CHH-6), 3.99 (dt, J = 6.9, 9.7 Hz, 1 H, CHHO), 4.59 (t, J = 3.3 Hz, 1 H, CHO), 7.08 (d, J = 5.2 Hz, 1 H, CH), 7.34 (d, J = 5.2 Hz, 1 H, CH), 7.45 (dd, J = 1.7, 4.5 Hz, 2 H, CH), 8.62 (dd, J = 1.7, 4.5 Hz, 2 H, CH) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 19.4 (CH_2-4), 25.4 (CH_2-5), 29.3 (CH_2), 30.5 (CH_2-3), 62.0 (CH_2-6), 67.2 (CH_2O), 98.6 (CHO), 123.4 (2×CH), 125.4 (CH), 130.2 (CH), 135.9 (C), 136.9 (C), 142.1 (C), 149.8 (2 × CH) ppm. EI-MS (positive mode): m/z (%) = 289.2 (26) $[M]^+$, 187.2 (100), 175.1 (72), 85 (74). $C_{16}H_{19}NO_2S$ (289.4): calcd. C 66.41, H 6.62, N 4.84; found C 66.65, H 6.44, N 5.04.

4-{5-Bromo-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]thiophen-2-yl}pyridine (38): To a solution of **37** (5.78 g, 20.0 mmol) in anhydrous DMF (20 mL), a solution of NBS (4.27 g, 24.0 mmol) in anhydrous DMF (20 mL) was added dropwise, and the mixture was stirred at room temperature for 24 h in the dark. The mixture was then poured into crushed ice, extracted with $CHCl_3$ (2 × 200 mL), washed with 10% aq. KOH (2× 100 mL), water (3× 100 mL), and dried with $MgSO_4$. The solvents were evaporated under reduced pressure and the residue was filtered through SiO_2 (200 mL) eluting with hexane/EtOAc (1:1) to give the title compound (R_f = 0.12) as a yellow oil; yield 5.2 g (76%; according to HPLC analysis, ca. 7% of the initial substance remained). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43–1.84 (m, 6 H, 3× CH_2, 3/4/5-H), 2.94 (t, J = 6.6 Hz, 2 H, CH_2), 3.42–3.51 (m, 1 H, C*H*H-6), 3.61 (dt, J = 6.7, 9.7 Hz, 1 H, C*H*HO), 3.67–3.76 (m, 1 H, CH*H*-6), 3.96 (dt, J = 6.7, 9.7 Hz, 1 H, CH*H*O), 4.58 (t, J = 3.2 Hz, 1 H, CHO), 7.05 (s, 1 H, CH), 7.39 (dd, J = 1.7, 4.5 Hz, 2 H, CH), 8.62 (dd, J = 1.7, 4.5 Hz, 2 H, CH) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 19.4 (CH_2-4), 25.4 (CH_2-5), 29.2 (CH_2), 30.5 (CH_2-3), 62.1 (CH_2-6), 67.0 (CH_2O), 98.7 (CHO), 112.5 (C-Br), 123.2 (2× CH), 132.9 (CH), 137.4 (C), 137.7 (C), 141.0 (C), 149.9 (2× CH) ppm. CI-MS (NH_3, positive mode): m/z (%) = 370.3 and 368.3 (100) $[M + H]^+$. HRMS (ESI, positive mode): calcd. for $C_{16}H_{18}BrNO_2S$ $[M + H]^+$ 368.0314; found 368.0315;

4-{4′-Bromo-5′-methyl-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-[2,2′]bithiophen-5-yl}pyridine (39): Bromide **38** (5.52 g, 15.0 mmol), $[Pd(dba)_2]$ (173 mg, 0.3 mmol), Ph_3P (315 mg, 1.2 mmol), and boronic acid **36**[21d,21e] (3.65 g, 16.5 mmol) were loaded into a Schlenk flask fitted with a reflux condenser and a bubble-counter. The flask was evacuated and flushed with argon several times. THF (75 mL) and 20% aq. Na_2CO_3 (75 mL) were added and the mixture was heated to reflux (bath temp. 78 °C) for 18 h. After dilution with EtOAc (75 mL), the organic layer was separated, washed with brine, dried, and evaporated under reduced pressure. The title compound was isolated as a yellow oil (6.35 g, 91%) by chromatography (200 g of SiO_2) eluting with hexane/EtOAc (2:1→1:1); R_f = 0.11 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.86 (m, 6 H, 3× CH_2, 3/4/5-H), 2.40 (s, 3 H, CH_3), 2.98 (t, J = 6.7 Hz, 2 H, CH_2), 3.42–3.52 (m, 1 H, C*H*H-6), 3.60–3.78 (m, 2 H, C*H*HO and CH*H*-6), 4.00 (dt, J = 6.7, 9.6 Hz, 1 H, CH*H*O), 4.61 (t, J = 3.3 Hz, 1 H, CHO), 7.00 (s, 1 H, CH), 7.09 (s, 1 H, CH), 7.46 (dd, J = 1.7, 4.5 Hz, 2 H, CH), 8.62 (dd, J = 1.7, 4.5 Hz, 2 H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8 (CH_3), 19.3 (CH_2-4), 25.3 (CH_2-5), 29.4 (CH_2), 30.5 (CH_2-3), 62.0 (CH_2-6), 67.0 (CH_2O), 98.7 (CHO), 109.7 (C), 123.3 (2× CH), 126.2 (CH), 126.7 (CH), 133.8 (2× C), 134.9 (C), 136.3 (C), 138.1 (C), 141.7 (C), 149.9 (2× CH) ppm. ESI-MS (positive mode): m/z (%) = 466.0 and 464.0 (100) $[M + H]^+$. HRMS (ESI, positive mode): calcd. for $C_{21}H_{22}BrNO_2S_2$ $[M + H]^+$ 464.0348; found 464.0358.

***tert*-Butyl *N*-Methyl-*N*-[2-(4-{3-[2-(tetrahydro-2*H*-pyran-2-yloxy)-ethyl]thiophen-2-yl}phenoxy)ethyl]carbamate (42):** To a solution of **34** (3.93 g, 13.5 mmol) in anhydrous THF (70 mL), *n*BuLi (2.5 M in hexane, 5.94 mL, 14.9 mmol) was added dropwise at –78 °C under argon, and the mixture was stirred for 1 h at –78 °C. Then $B(OiPr)_3$ (3.81 g, 20.3 mmol) was added and the mixture was stirred for 1 h at –78 °C and for 2 h at room temperature. Water (0.5 mL) was added, followed by compound **40**[10] (3.39 g, 9.00 mmol), Ph_3P (189 mg, 0.72 mmol), $[Pd(dba)_2]$ (104 mg, 0.18 mmol), and 20% aq. Na_2CO_3 (70 mL), and the mixture was heated at 78 °C (bath temp.) for 18 h in a flask equipped with a reflux condenser and a bubble-counter. The mixture was diluted with EtOAc (100 mL) and the organic phase was separated, washed with brine (50 mL), dried, and evaporated under reduced pressure. Chromatography (150 g of SiO_2) with hexane/EtOAc (8:1→4:1) afforded the title compound (3.7 g, 90%) as a colorless oil; R_f = 0.12 (hexane/EtOAc, 4:1). HPLC [70→100% A (30→0% B) for 0–20 min]: t_R = 10.9 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*Bu), 1.48–1.89 (m, 6 H, 3× CH_2, 3/4/5-H), 2.93 (t, J = 7.0 Hz, 2 H, C$H_2$$CH_2O$), 2.99 (s, 3 H, CH_3N), 3.40–3.49 (m, 1 H, C*H*H-6), 3.54–3.67 (m, 3 H, OCH_2CH_2N and CH_2CHHO), 3.70–3.79 (m, 1 H, CH*H*-6), 3.94 (dt, J = 7.0, 9.6 Hz, 1 H, CH_2CH*H*O), 4.06–4.17 (m, 2 H, OCH_2CH_2N), 4.58 (t, J = 3.3 Hz, 1 H, CHO), 6.88–6.96 (m, 2 H, 2× CH), 7.02 (d, J = 5.2 Hz, 1 H, CH), 7.18 (d, J = 5.2 Hz, 1 H, CH), 7.36–7.43 (m, 2 H, CH) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$): δ (2 rotamers) = 19.5 (CH_2-4), 25.5 (CH_2-5), 28.5 (3× CH_3), 29.1 (CH_2), 30.6 (CH_2-3), 35.4/36.3 (CH_3N), 48.3 (CH_2N), 62.0 (CH_2-6), 66.1/66.9 (OCH_2), 67.6 (CH_2OTHP), 79.7 (C), 98.5 (CHO), 114.3 (2× CH), 123.0 (CH), 126.9 (C), 129.5 (2× CH), 130.6 (CH), 134.2 (C), 138.8 (C), 155.4/155.7 (CO), 157.9/158.1 (CO) ppm. ESI-MS (positive mode): m/z (%) = 484.2 (100) $[M + Na]^+$, 462.2 (6) $[M + H]^+$. $C_{25}H_{35}NO_5S$ (461.6) calcd. C 65.05, H 7.64, N 3.03; found C 65.33, H 7.39, N 2.90.

***tert*-Butyl *N*-[2-(4-{5-Iodo-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-thiophen-2-yl}phenoxy)ethyl]-*N*-methyl Carbamate (43):** To a solution of **42** (3.55 g, 7.7 mmol) in benzene (30 mL), HgO (2.0 g, 9.2 mmol) and iodine (2.37 g, 9.2 mmol) were added alternately in small portions. The mixture was stirred at room temperature for 4 h, and then filtered through a Celite pad, washing with toluene (100 mL). The combined organic solutions were washed with sat. aq. $Na_2S_2O_3$ (2× 50 mL), water (3× 50 mL), and dried. After evaporation of the solvents under reduced pressure, the residue was filtered through SiO_2 (100 g) eluting with hexane/EtOAc (4:1) to give the title compound (4.19 g, 92%) as a yellowish oil; R_f = 0.09. HPLC [70→100% A (30→0% B) for 0–20 min]: t_R = 15.5 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 1.49–1.86 (m, 6 H, 3× CH_2, 3/4/5-H), 2.87 (t, J = 6.9 Hz, 2 H, C$H_2$$CH_2O$), 2.99 (s, 3 H, CH_3N), 3.42–3.50 (m, 1 H, C*H*H-6), 3.52–3.60 (m, 1 H,

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CH_2CHHO), 3.62 (t, J = 5.0 Hz, 3 H, OCH_2CH_2N), 3.69–3.78 (m, 1 H, CH*H*-6), 3.90 (dt, J = 6.9, 9.7 Hz, 1 H, CH_2CHHO), 4.07–4.17 (m, 2 H, OCH_2CH_2N), 4.57 (t, J = 3.4 Hz, 1 H, CHO), 6.90–6.95 (m, 2 H, 2× CH), 7.17 (s, 1 H, CH), 7.31–7.36 (m, 2 H, CH) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$): δ (2 rotamers) = 19.4 (CH_2-4), 25.5 (CH_2-5), 28.5 (3× CH_3), 28.7 (CH_2), 30.6 (CH_2-3), 35.4/36.2 (CH_3N), 48.3 (CH_2N), 62.0 (CH_2-6), 66.1/66.8 (OCH_2), 67.3 (CH_2OTHP), 70.6 (C-I), 79.6 (C), 98.5 (CHO), 114.4 (2× CH), 125.8 (C), 130.5 (2× CH), 136.4 (C), 139.3 (CH), 145.0 (C), 155.3/155.6 (CO), 158.2/158.4 (CO) ppm. ESI-MS (positive mode): m/z (%) = 610.1 (100) $[M + Na]^+$. HRMS (ESI, positive mode): calcd. for $C_{25}H_{34}INO_5S$ $[M + Na]^+$ 610.1100; found 610.1095.

***tert*-Butyl *N*-[2-(4-{4′-Bromo-5′-methyl-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-(2,2′)bithiophen-5-yl}phenoxy)ethyl]-*N*-methyl carbamate (44):** According to the procedure described for the synthesis of **39**, iodide **43** (4.0 g, 6.8 mmol), $[Pd(dba)_2]$ (78 mg, 0.14 mmol), Ph_3P (142 mg, 0.54 mmol), and boronic acid **36**[21d,21e] (1.8 g, 8.2 mmol) gave the title compound (4.15 g, 96%) as a yellow oil after chromatography (150 g of SiO_2) eluting with hexane/EtOAc (4:1); R_f = 0.12. HPLC [70→100% A (30→0% B) for 0–20 min, 100% A for 20–25 min]: t_R = 22.9 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 1.49–1.87 (m, 6 H, 3× CH_2, 3/4/5-H), 2.39 (s, 3 H, CH_3), 2.90 (t, J = 6.9 Hz, 2 H, CH_2CH_2O), 3.00 (s, 3 H, CH_3N), 3.42–3.52 (m, 1 H, C*H*H-6), 3.56–3.66 (m, 3 H, OCH_2CH_2N, CH_2CHHO), 3.70–3.80 (m, 1 H, CH*H*-6), 3.95 (dt, J = 7.0, 9.6 Hz, 1 H, CH_2CHHO), 4.06–4.17 (m, 2 H, OCH_2CH_2N), 4.60 (t, J = 3.3 Hz, 1 H, CHO), 6.89–6.96 (m, 2 H, CH), 6.93 (s, 1 H, CH), 7.05 (s, 1 H, CH), 7.38–7.43 (m, 2 H, CH) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$): δ (2 rotamers) = 14.8 (CH_3), 19.5 (CH_2-4), 25.5 (CH_2-5), 28.5 (3× CH_3), 29.2 (CH_2), 30.6 (CH_2-3), 35.4/36.2 (CH_3N), 48.3 (CH_2N), 62.0 (CH_2-6), 66.1/66.9 (OCH_2), 67.3 (CH_2OTHP), 79.7 (C), 98.5 (CHO), 109.4 (C-Br), 114.5 (2× CH), 125.3 (CH), 126.2 (CH), 130.4 (2× CH), 132.7 (C), 133.6 (C), 134.5 (C), 135.1 (C), 137.7 (C), 138.3 (C), 155.4/155.7 (CO), 158.1/158.2 (CO) ppm. ESI-MS (positive mode): m/z (%) = 660.1 and 658.1 (100) $[M + Na]^+$. HRMS (ESI, positive mode): calcd. for $C_{30}H_{38}BrNO_5S_2$ $[M + Na]^+$ 658.1267 and 660.1248; found 658.1268 and 660.1246.

4-{5′-Methyl-4′-(heptafluorocyclopent-1-enyl)-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,2′-bithiophen-5-yl}pyridine (47): To a vigorously stirred mixture of bromide **39** (0.93 g, 2.0 mmol) in anhydrous THF (20 mL), *n*BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Cooled perfluorocyclopentene (2.7 mL, 20.0 mmol) was quickly added and the mixture was stirred for 1 h at –78 °C and then quenched with brine. The reaction mixture was diluted with EtOAc (15 mL), dried, and evaporated under reduced pressure. Chromatography (100 g of SiO_2) with hexane/EtOAc (1:1) afforded the title compound (0.30 g, 25%) as a yellowish oil; R_f = 0.13. HPLC [30→100% A (70→0% B) for 0–25 min]: t_R = 19.4 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.86 (m, 6 H, 3× CH_2, 3/4/5-H), 2.46/2.47 (s, 3 H, CH_3), 2.99 (t, J = 6.6 Hz, 2 H, CH_2), 3.42–3.52 (m, 1 H, C*H*H-6), 3.62–3.78 (m, 2 H, C*H*HO and CH*H*-6), 4.01 (dt, J = 6.6, 9.6 Hz, 1 H, CH*H*O), 4.62 (t, J = 3.2 Hz, 1 H, CHO), 7.13 (s, 1 H, CH), 7.15 (s, 1 H, CH), 7.44 (dd, J = 1.7, 4.6 Hz, 2 H, CH), 8.63 (dd, J = 1.7, 4.6 Hz, 2 H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6/14.7 (CH_3), 19.3 (CH_2-4), 25.4 (CH_2-5), 29.4 (CH_2), 30.5 (CH_2-3), 62.1 (CH_2-6), 67.7 (CH_2O), 98.7 (CHO), 120.4 (C), 122.9 (CH), 123.3 (2× CH), 127.5 (CH), 135.1 (C), 135.5 (C), 135.6 (C), 138.1 (C), 141.5 (C), 143.0 (C), 150.1 (2× CH) ppm; Due to low intensities, the split signals of the fluorinated carbon atoms were not detected. ESI-MS (positive mode): m/z (%) = 578.1 (100) $[M + H]^+$. HRMS (ESI, positive mode): calcd. for $C_{26}H_{22}F_7NO_2S_2$ $[M + H]^+$ 578.1058; found 578.1063.

Photochromic Compound 52: To a solution of bromide **44** (0.64 g, 1.0 mmol) in anhydrous THF (15 mL), *n*BuLi (2.5 M in hexane, 0.4 mL, 1.0 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. A solution of heptafluorocyclopentene **47** (0.29 g, 0.5 mmol) in THF (9 mL) was added and the mixture was stirred for 2 h at –78 °C and for 1 h at room temperature, followed by addition of brine (1 mL). The organic layer was separated, dried with Na_2SO_4, and evaporated under reduced pressure. The title compound was isolated by chromatography (100 g of SiO_2) with hexane/EtOAc (1:1→1:3) as eluent to give **52** (0.35 g, 62%) as a green foam. HPLC [30→100% A (70→0% B) in 25 min]: t_R (OF) = 13.9 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (open form, mixture of rotamers) = 1.47 (s, 9 H, *t*Bu), 1.49–1.86 (m, 12 H, 6× CH_2), 1.95 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 2.91 (t, J = 6.9 Hz, 2 H, CH_2), 2.99 (t, J = 6.8 Hz, 2 H, CH_2), 3.00 (s, 3 H, CH_3N), 3.44–3.50 (m, 2 H, 2× C*H*H-6), 3.59–3.65 (m, 3 H, CH_2N and C*H*HOTHP), 3.65–3.69 (m, 1 H, C*H*HOTHP), 3.72–3.80 (m, 2 H, 2× CH*H*-6), 3.95 (dt, J = 6.9, 9.5 Hz, 1 H, CH*H*OTHP), 4.01 (dt, J = 6.8, 9.6 Hz, 1 H, CH*H*OTHP), 4.08–4.17 (m, 2 H, CH_2O), 4.59–4.64 (m, 2 H, 2× CHO), 6.91–6.95 (m, 2 H, 2× CH), 7.09 (s, 1 H, CH), 7.10 (s, 1 H, CH), 7.14 (s, 1 H, CH), 7.16 (s, 1 H, CH), 7.34–7.42 (m, 2 H, 2× CH), 7.45 (dd, J = 1.5, 4.5 Hz, 2 H, CH), 8.63 (dd, J = 1.5, 4.5 Hz, 2 H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (open form, mixture of rotamers) = 14.2 (CH_3), 14.5/14.6 (CH_3), 19.5 (2× CH_2-4), 25.4/25.5 (2× CH_2-5), 29.2/29.4 (2× CH_2), 30.6 (2× CH_2-3), 35.4/36.3 (CH_3N), 48.3 (CH_2N), 62.1 (2× CH_2-6), 66.2/66.9 (OCH_2), 67.1 (CH_2OTHP), 67.4 (CH_2OTHP), 79.7 (C), 98.6/98.7 (2× CHO), 114.0 (C), 114.5 (2× CH), 122.0 (CH), 123.0 (CH), 123.2 (3× CH), 125.4 (C), 125.6 (C), 126.7/127.1 (2× CH), 130.4 (2× CH), 133.3 (C), 134.8 (C), 135.2 (2× C), 135.8 (C), 135.9 (C), 138.0 (2× C), 138.6 (C), 139.1 (CH), 140.3 (C), 141.2 (C), 141.5 (C), 149.9 (2× CH), 155.4/155.7 (CO), 158.2/158.3 (CO) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –110.04 (m, 2 F), –110.14 (m, 2 F), –131.82 (quint, J = 5.7 Hz, 2 F) ppm. ESI-MS (positive mode): m/z (%) = 1115.3 (100) $[M + H]^+$. HRMS (ESI, positive mode): calcd. for $C_{56}H_{60}F_6N_2O_7S_4$ $[M + H]^+$ 1115.3260; found 1115.3259.

Photochromic Compound 54: A solution of **52** (0.22 g, 0.20 mmol) and PPTS (10 mg, 0.04 mmol) in EtOH (10 mL) was stirred at 55 °C for 7 d under argon. After evaporation of the solvent, the title compound was isolated as a blue foam by chromatography (100 g of SiO_2) with CH_2Cl_2/MeOH (10:1) as eluent. Yield 0.165 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (open form, mixture of rotamers) = 1.47 (s, 9 H, *t*Bu), 1.97 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3), 2.88 (t, J = 6.5 Hz, 2 H, CH_2), 2.97 (t, J = 6.5 Hz, 2 H, CH_2), 2.99 (s, 3 H, CH_3N), 3.58–3.66 (m, 2 H, CH_2N), 3.85 (t, J = 6.5 Hz, 2 H, CH_2OH), 3.93 (t, J = 6.5 Hz, 2 H, CH_2OH), 4.07–4.17 (m, 2 H, CH_2O), 6.90–6.97 (m, 2 H, 2× CH), 7.05 (s, 1 H, CH), 7.09 (s, 1 H, CH), 7.11 (s, 1 H, CH), 7.15 (s, 1 H, CH), 7.35–7.41 (m, 2 H, 2× CH), 7.41–7.45 (m, 2 H, CH), 8.56–8.68 (m, 2 H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.5 (CH_3), 14.6 (CH_3), 28.5 (3× CH_3), 31.9 (CH_3N), 32.1 (2× CH_2), 48.3 (CH_2N), 62.5 (2× CH_2OH), 62.8 (CH_2O), 79.8 (C), 114.6 (2× CH), 122.3 (CH), 123.3 (3× CH), 125.4 (C), 125.6 (C), 126.2 (CH), 126.7 (CH), 130.5 (2× CH), 133.8 (C), 134.6 (2× C), 134.7 (C), 135.4 (C), 135.5 (C), 136.4 (2× C), 137.6 (2× C), 139.1 (C), 140.5 (C), 141.4 (C), 141.6 (C), 149.8 (2× CH), 158.3 (C=O), 158.4 (C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.96 (m, 2 F), –110.04 (m, 2 F), –131.79 (t, J = 5.2 Hz, 2 F) ppm. ESI-MS (positive mode): m/z (%) = 947.1 (100) $[M + H]^+$. HRMS (ESI, positive mode): calcd. for $C_{46}H_{44}F_6N_2O_5S_4$ $[M + H]^+$ 947.2110; found 947.2114.

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Photochromic Compound 57: Compound **54** (14 mg, 15 μmol) was stirred with β-sulfopropionic acid anhydride (**55**; 4 mg, 30 μmol) under argon in anhydrous THF at room temperature for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography (20 g of SiO_2) eluting with CH_2Cl_2/MeOH (2:1) to afford the title compound (15 mg, 83%) as a green foam. HPLC [30→100% A (70→0% B) in 25 min; detection at the isosbestic point (362 nm)]: t_R (OF) = 12.4 min (78%), t_R (CF) = 12.7 min (22%).

57-OF: ^{1}H NMR (300 MHz, CD_3OD): δ = 2.03 (2 s, 6 H, CH_3), 2.59–2.87 (m, 4 H, CH_2CO), 2.71 (s, 3 H, CH_3N), 2.95–3.14 (m, 6 H, 2× CH_2, CH_2N), 3.45–3.50 (m, 4 H, 2× CH_2S), 4.16–4.26 (m, 2 H, CH_2O), 4.27–4.40 (m, 4 H, CH_2OCO), 7.03–7.16 (m, 4 H, CH), 7.22 (s, 1 H, CH), 7.25 (s, 1 H, CH), 7.34–7.50 (m, 2 H, CH), 7.53–7.63 (m, 2 H, CH), 8.52–8.68 (m, 2 H, CH) ppm. ESI-MS (negative mode): *m/z* (%) = 1117.2 (100) $[M - H]^-$, 558.1 (91) $[M - 2H]^{2-}$. HRMS (ESI, negative mode): calcd. for $C_{47}H_{44}F_6N_2O_{11}S_6$ $[M - 2H]^{2-}$ 558.0514; found: 558.0520

Compound 57-CF: Isolated after irradiation of the methanolic solution containing compound **57**-OF with a UV-lamp (365 nm) followed by evaporation in vacuo, column chromatography on SiO_2 ($CHCl_3$/MeOH/H_2O, 75:25:3) and lyophilization. ^{1}H NMR (600 MHz, CD_3OD): δ = 2.18 (s, 6 H, CH_3), 2.49 (m, 2 H, CH_2CO), 2.71 (s, 3 H, CH_3N), 2.72 (t, J = 7 Hz, 2 H, CH_2CO), 2.86 (m, 2 H, CH_2S), 3.02 t (J = 7 Hz, 2 H, CH_2S), 3.07 (t, J = 6 Hz, 2 H, CH_2C_{Ar}), 3.12 (t, J = 7 Hz, 2 H, CH_2C_{Ar}), 3.34 (t, J = 6 Hz, 2 H, CH_2N), 4.24 (t, J = 6 Hz, 2 H, CH_2O), 4.30 [t, J = 6 Hz, 2 H, $(NCH_2)CH_2O$], 4.35 (t, J = 7 Hz, 2 H, CH_2O), 6.57 (s, 1 H, CH=), 6.64 (s, 1 H, CH=), 7.12 (d, J = 8 Hz, 2 H, ArH), 7.40 (s, 1 H, ArH), 7.48 (s, 1 H, ArH), 7.49 (d, J = 8 Hz, 2 H, ArH), 7.62 (m, 2 H, 3-H in 4-pyridyl), 8.64 (m, 2 H, 2-H in 4-pyridyl) ppm. ^{19}F NMR (282 MHz, CD_3OD): δ = –135.0 (m, 2 F), –114.0 (m, 4 F) ppm.

Supporting Information (see footnote on the first page of this article): Syntheses and properties of early precursors and side-products (compounds **4**–**31**, **41**, **45**, and **48**–**50**).

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