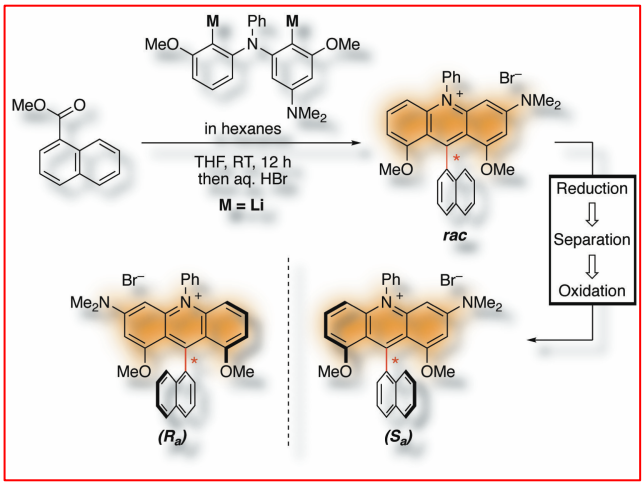
Configurationally Stable Atropisomeric Acridinium Fluorophores

Christian Fischer
Christof Sparr*

Department of Chemistry,
University of Basel,
St. Johanns-Ring 19,
4056 Basel, Switzerland.

christof.sparr@unibas.ch

In Memoriam Kurt Mislow.



Abstract Arylated heterocyclic fluorophores are particularly useful scaffolds for numerous applications, such as bioimaging or synthetic photochemistry. While variation of the substitution pattern at the heterocycle and aryl groups allows dye modulation, also the bond rotational barriers are strongly affected. Unsymmetrically substituted ring systems of rotationally restricted arylated heterocycles therefore lead to configurationally stable atropisomeric fluorophores. Herein, we describe these characteristics by determining the properties and configurational stability of configurationally stable, tri-*ortho*-substituted, atropisomeric naphthyl-acridinium fluorophores. A significant barrier to rotation of >120 kJmol^{-1} was measured, which renders these dyes and related compounds distinct atropisomers with stereoisomer-specific properties over a broad temperature range.

Key words atropisomerism, heterocycles, fluorophores, acridinium salts, barrier to rotation

The absorption and emission characteristics, brightness, excited state life times and redox potentials are important attributes for fluorophores used in imaging, synthetic photochemistry and other applications.[1] Modulation of these properties is typically achieved by altering the substitution pattern of an established arylated heterocyclic fluorophore scaffold. However, these adjustments also impact the symmetry and the conformational behavior of fluorophores such as fluorescein- and rhodamine-derivatives (Figure 1a vs. 1b).[2,3] With three or four *ortho*-substituents, the rotation is typically sufficiently hindered in both directions to provide atropisomers that are configurationally stable at ambient temperature and under physiological conditions. Conjugation to a typical biomolecule or other moieties with stereocenters would hence provide diastereoisomers, and in cases of racemic atropisomers, diastereoisomeric mixtures, which can lead to misinterpretation or unnecessarily perplexing analyses. Furthermore, utilizing the rotationally restricted dyes as probes for biological samples may also result in atropisomer-specific interactions as with other distinct stereoisomers, such as bioactive compounds.

Furthermore, isomer-specific chiroptical properties and biological activities can be expected, as observed in the helically shaped [4]heterohelicenium dyes (DMQA, Figure 1c) pioneered by Laursen and Lacour.[4]

Considering the stereodynamic behavior of the acridinium dye obtained from the twofold nucleophilic aromatic substitution with 1-phenylethylamine, featuring a barrier to rotation about C(sp^3)–N(sp^2) bond of $\Delta G^{\ddagger}_{298\,K}$ = 51.4 kJ mol^{-1}, (Figure 1d),[5,6] we anticipated that the acridinium dyes with a tri-*ortho* substitution

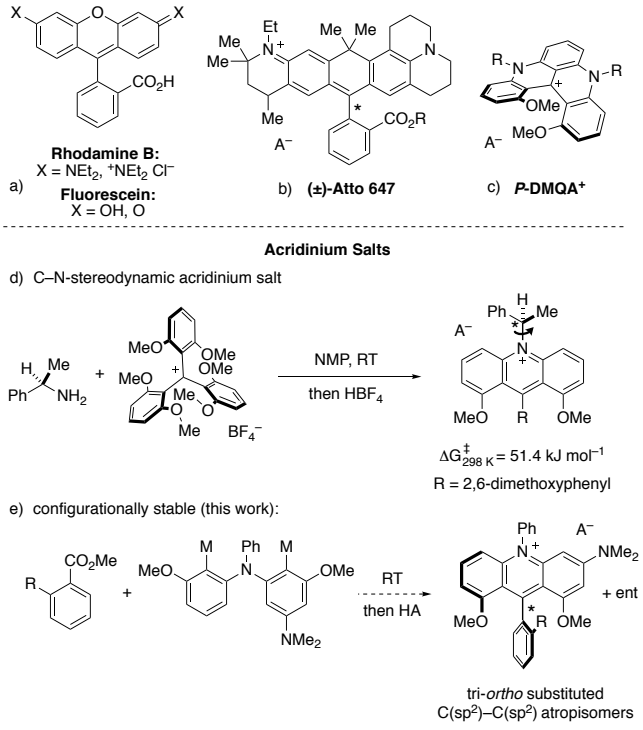
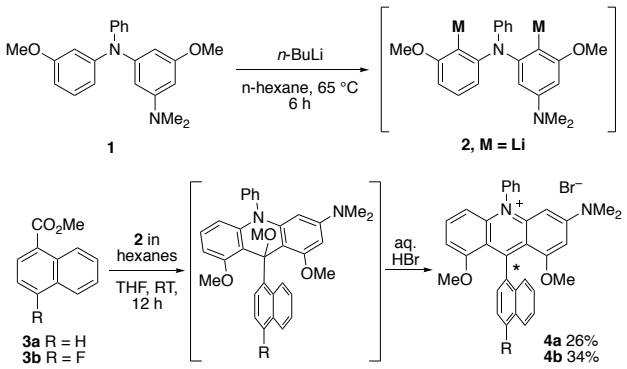


Figure 1: Commonly used symmetric a) rhodamine B and fluorescein, b) racemic ATTO 647 dyes. c) Helical chiral DMQA salt. Acridinium salts: d) C–N stereodynamic acridinium salt, e) configurationally stable atropisomeric acridinium fluorophore with hindered rotation about the C(sp^2)-C(sp^2) bond.

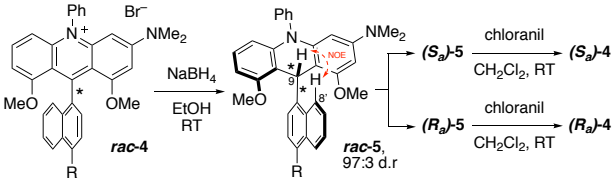
with respect to the aryl–heterocycle bond would provide configurationally stable atropisomers at ambient temperature. To investigate the conformational behavior, we envisaged their synthesis directly from carboxylic acid esters by employing 1,5-bifuctional organometallic reagents, thus allowing expeditious variation of the C9-substituent.[7,8] Furthermore, by the double directed *ortho*-metalation (dDoM) strategy,[7] an unsymmetrically substituted acridinium system with 1,9-dimethoxy-*peri*-substitution is readily accessible without a preceding halogenation and halogen-metal exchange (Figure 1e). Moreover, we expected that the di-*peri*-substitution of the acridinium moiety and the 1-naphtyl group from the corresponding carboxylic acid methyl esters would further increase the barrier to rotation about the C(sp²)-C(sp²) bond and thus lead to configurationally stable atropisomeric fluorophores. With the presence of the NMe_2-group we anticipated a bathochromic shift in absorption and emission as well as an attenuation of the redox properties.[7,8a]

To prepare the preferred acridinium atropisomers, unsymmetrically substituted triarylamine **1** was treated with *n*-butyllithium in *n*-hexane at 65 °C to form 1,5-bifunctional organolithium reagent **2** by a double directed *ortho*-metalation (dDoM, Scheme 1 top).[7,9] The addition of **2** to methyl 1-naphthoates **3a** and **3b** and subsequent treatment with aqueous hydrobromic acid, thus provided racemic acridinium bromide salts **4a** and **4b** concisely, but with low yields of 26% and 34%, respectively (Scheme 1 bottom).[10-12]



Scheme 1: Double directed *ortho*-metalation on tertiary amine **1** allows the synthesis of 1,5-bifunctional organolithium reagent **2**. Ensuing addition to ester **3a** or **3b** and in-situ dehydration using aq. HBr allows the direct transformation into atropisomeric acridinium bromide salts.

With tri-*ortho*-substituted acridinium dyes in hand, we set out to investigate the configurational stability by separating the racemic mixtures into their atropo-enantiomers. By a reduction with $NaBH_4$, the dyes **4** were effortlessly converted into their corresponding *leuco*-form **5** in a diastereomeric ratio of 97:3 (Scheme 2). Interestingly, HPLC analysis on a chiral stationary phase established that the C(sp³)–N(sp²) bond of *leuco*-form **5** is sufficiently rotationally restricted, which allows the separation by chromatography at ambient temperature (Chiracel® OD-H, *n*-heptane:*i*-PrOH 95:5).[13-15] Notably, the separated enantiomers of the *leuco*-form **5** showed pronounced configurational stability over several days and were also chemically inert to aerobic oxidation at RT. To prepare enantioenriched acridinium dyes **4a** and **4b**, we hence employed chloranil and individually reoxidized the separated enantiomers of the *leuco*-form **5**.[17] A 90:10 enantiopurity of the dyes **4a** and **4b** was obtained by this method (determined by HPLC of *leuco*-form samples prepared as previously).



Scheme 2: Reduction of the racemic dye **4a** and **4b** by $NaBH_4$,[16] followed by separation and individual oxidation with chloranil gave access to both enantiomers of the atropisomeric fluorophore in 90:10 e.r.

We next investigated the properties of the enantioenriched dyes **4a** and **4b** by UV and ECD spectroscopy and found pronounced Cotton effects around 240, 260 and 310 nm (Figure 2).[10,11] Strong bathochromic shifts in absorption and emission spectra and alleviated redox potentials of the diamino-substituted acridinium salts as compared to the Fukuzumi acridinium- (MesMeAcr) or 9-mesityl-1,3,6,8-tetramethoxy-10-phenylacridinium salt were measured.[11–12,18] Furthermore, a remarkable configurational stability of the atropisomeric acridinium fluorophores was determined in racemization experiments of **4a** and **4b** in cyclohexanol at 120 °C (Table 1).[19] In both cases, the tri-*ortho*-substitution leads to exceptional configurationally stability and significant bond rotational barriers of $\Delta G^{\ddagger}_{298\,K}$ = 124 kJ mol⁻¹ and $\Delta G^{\ddagger}_{298\,K}$ = 127 kJ mol⁻¹.[20]

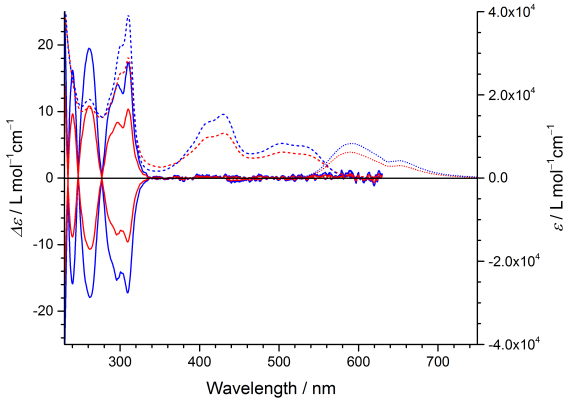
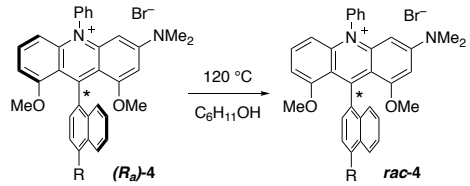


Figure 2: ECD spectroscopy of both enantiomers of **4a** (red) and **4b** (blue, full lines, y-axis: $\Delta\varepsilon$) and corresponding UV spectrum (dashed lines, y-axis: ε) and normalized emission spectrum (dotted lines).



#	k_{rac}	$t_{1/2_{393\,K}}$	$\Delta G^{\ddagger}_{393\,K}$
4a	6.00·10⁻⁴ s⁻¹	19 min	124 kJ mol⁻¹
4b	2.16·10⁻⁴ s⁻¹	54 min	127 kJ mol⁻¹

Table 1: Determination of the configurational stability of atropisomeric acridinium dyes **4a** and **4b**.

Having confirmed the high configurational stability of atropisomeric acridinium dyes, applications for novel optical materials, diastereomerically enriched conjugates or atropisomer-specific bioimaging probes are anticipated. Furthermore, fluorophore modulation, particularly at the acridinium 9-position, is readily achieved by the directed *ortho*-metalation strategy for the formation of 1,5-bifunctional organometallic reagents.

In conclusion, substitution of heterocyclic fluorophores such as acridinium dyes strongly impacts the conformational behavior and hence provides an avenue towards atropisomers with a notable configurational stability over a broad temperature range. Having evaluated the bond rotational barriers, atropisomeric fluorophores can be strategically implemented into diagnostic tools, imaging, material sciences or photocatalysis. Current efforts in our group focus on the stereoselective synthesis of atropoisomeric fluorophores and their applications.[21]

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References and Notes

(1) (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166. (b) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed.* **2018**, doi: 10.1002/anie.201709766. (c) Terai, T.; Nagano, T.; *Pflugers Arch. EJP* **2013**, *465*, 347–359. (d) Ni, M.; Zhuo, S.; So, P. T. C.; Yu, H. *J. Biophotonics* **2017**, *10*, 11–23.

(2) (a) Heagy, M. D. In Chemosensors: Principles, Strategies, and Applications; New Fluorophore Design; Wang, B.; Anslyn, E. V., Eds.; John Wiley & Sons, Inc.: Hoboken, **2011**, 253–273. (c) The Molecular Probes® Handbook; Johnson, I.; Spence, M. T. Z., Eds.; 11th ed.; Life Technologies Corporation; **2010**. (d) Zilles, A.; Arden-Jacob, J.; Drexhage, K.-H.; Kemnitzer, N. U.; Hammers-Schneider, M. PCT Int. Appl. WO2005/003086, **2005**. (e) Kolmakov, K.; Belov, V. N.; Wurm, C. A.; Harke, B.; Leutenegger, M.; Eggeling, C.; Hell, S. W. *Eur. J. Org. Chem.* **2010**, 3593–3610.

(3) Early work on biphenyls with optical activity as a consequence of restricted rotation about a single bond: (a) Mislow, K.; Rutkin, P.; Lazarus, A. K. *J. Am. Chem. Soc.* **1957**, *79*, 2974–2975; (b) Mislow, K. *Trans. N. Y. Acad. Sci.* **1957**, *19*, 298–314. (c) Stereoisomerism and local chirality: Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106,* 3319–3328. (d) Atroposelective arene formation: Link, A.; Sparr, C. *Chem. Soc. Rev.* **2018**, *47*, 3804–3815; Zilate, B.; Castrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981–2988.

(4) (a) Laursen, B. W.; Krebs, F. C. *Angew. Chem. Int. Ed.* **2000**, *39*, 2432–2434. (b) Herse, C.; Bas, D.; Krebs, F. C.; Bürgi, T.; Weber, J.; Wesolowski, T.; Laursen, B. W.; Lacour, *Angew. Chem. Int. Ed.* **2003**, *42*, 3162–3166. (c) Hernández Delgado, I.; Pascal, S.; Besnard, C.; Voci, S.; Bouffier, L.; Sojic, N.; Lacour, J. *Chem. Eur. J.* **2018**, doi: 10.1002/chem.201801486. (d) Bauer, C.; Duwald, R.; Labrador, G. M.; Pascal, S.; Lorente, P. M.; Bosson, J.; Lacour, J.; Rochaix, J.-D. *Org. Biomol. Chem.* **2018**, *16*, 919-923. (e) Elm, J.; Lykkebo, J.; Sørensen, T. J.; Laursen, B. W.; Mikkelsen, K. V. *J. Phys. Chem. A* **2011**, *115*, 12025–12033.

(5) (a) Laleu, B.; Herse, C.; Laursen, B. W.; Bernardinelli, G.; Lacour, J. *J. Org. Chem.* **2003**, *68*, 6304–6308. (b) Hindered rotation observed in pyridinium systems: Balaban, A. T.; Dinculescu, A.; *Tetrahedron* **1984**, *40*, 2547–2553. (c) Bosson, J.; Gouin, J.; Lacour, J. *Chem. Soc. Rev.* **2014**, *43*, 2824–2840.

(6) Ōki, M. In Topics in Stereochemistry: Recent Advances in Atropisomerism; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons, Inc.: Hoboken, **1983**, 1–82.

(7) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Fischer, C; Sparr, C. *Tetrahedron* **2018** doi: 10.1016/j.tet.2018.04.060.

(8) Formation of 1,5-bifunctional organometallic reagents by halogen-metal exchange and addition to carboxylic acid esters to form: (a) heterocyclic fluorophores: Fischer, C; Sparr, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 2436–2440; (b) atroposelective biaryls: Link, A.; Sparr, C. *Angew. Chem Int. Ed.* **2018**, *57*, 7136–7139. (c) arenes and acenes: Link, A.; Fischer, C.; Sparr, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 12163–12166. (d) Link, A.; Fischer, C.; Sparr, C. *Synthesis* **2017**, *49*, 397–402.

(9) **General procedure for the double directed *ortho*-metalation:** To a solution of bis(3-methoxyphenyl)-amine (160 µmol) in *n*-hexane (2.0 mL) was added a solution of *n*-butyllithium in hexanes (176 µL, 1.49 molL−1, 320 µmol) at RT. The mixture was stirred 6 h at 65 °C. The reaction mixture was directly used in the next step.

(10) **General procedure for the transformation of esters into acridinium salts:** To the reaction mixture of the metalated aryl aniline in *n*-hexane (160 µmol) at −20 °C was added a solution of carboxylic acid ester (100 µmol) in anhydrous THF (0.60 mL) and the reaction mixture was allowed to warm to RT over 12 h. Aqueous HBr (1.00 mL, 48%) was added, followed by water (20 mL) and the mixture was extracted by a $CHCl_3$:*i*-PrOH solution (4 × 10 mL; 85:15). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using 100% CH_2Cl_2 to CH_2Cl_2:MeOH 100:2 to 100:3 to 100:4 provided the product.

(11) **(±)-3-(Dimethylamino)-1,8-dimethoxy-9-(naphthalen-1-yl)-10-phenylacridinium bromide salt (4a):** Prepared according to the above general procedures using 5-methoxy-N^1-(3-methoxyphenyl)-N^3,N^3-dimethyl-*N*-phenylbenzene-1,3-diamine (55.8 mg, 160 µmol) and methyl 1-naphthoate (18.6 mg, 100 µmol). Purification provided a brown-red solid (14.4 mg, 26%, HPLC purity: 89% at 400 nm, decomp. at 131 °C): R_f 0.12 (CH_2Cl_2:MeOH 10:1); ν_{max} (neat): 3369w, 2925w, 2361w, 1623s, 1598s, 1497s, 1475s, 1427m, 1377m, 1349s, 1255s, 1168w, 1102s, 972m, 785s, 768s, 707m; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.95 (1H, d, ^3J 8.2, C5'*H*), 7.87–7.91 (3H, m, C4'*H*, C3"*H*, C5"*H*), 7.79–7.81 (1H, m, C4"*H*), 7.60 (1H, t, ^3J 8.4, C6*H*), 7.46–7.52 (4H, m, C3'*H*, C6'*H*, C2"*H*, C6"*H*), 7.41–7.42 (1H, m, C8'*H*), 7.34–7.37 (1H, m, C7'*H*), 7.09 (1H, d, ^3J 6.9, C2'*H*), 6.64 (1H, d, ^3J 8.0, C7*H*), 6.57 (1H, d, ^3J 8.8, C5*H*), 6.32 (1H, d, ^4J 1.2, C2*H*), 5.48 (1H, d, ^4J 1.3, C4*H*), 3.14 (3H, s, C1OCH_3), 3.12 (6H, br, N(CH_3)$_2$), 2.99 (3H, s, C8OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 161.1 (*C1*), 159.8 (*C8*), 157.3 (*C3*), 155.1 (*C9*), 145.3 (*C4a*), 142.0 (*C10a*), 140.0 (*C1'*), 138.7 (*C1"*), 136.4 (*C6*), 132.2 (*C4'a*), 132.2 (*C3"*), 132.1 (*C8'a*), 132.0 (*C5"*), 131.1 (*C4"*), 128.1 (*C5'*), 128.1 (*C2"*), 128.0 (*C6"*), 127.0 (*C4'*), 126.0 (*C7'*), 125.6 (*C6'*), 125.1 (*C8'*), 124.9 (*C3'*), 121.9 (*C2'*), 116.4 (*C9a*), 115.3 (*C8a*), 109.7 (*C5*), 106.0 (C7), 95.9 (C2), 89.1 (C4), 56.8 (C1OCH_3), 56.2 (C8OCH_3), 41.2 (N(CH_3)$_2$); ESI-MS: m/z calcd. for $C_{33}H_{29}N_2O_2^+$ 485.2224 found 485.2226 [M$^+$]. Luminescence spectroscopy (in MeCN): λ_{abs1}: 504 nm; λ_{abs2}: 431 nm; λ_{abs3}: 311 nm; ε_{abs1}: $8.5\cdot10^3$ L cm mol^{-1}; ε_{abs2}: $1.6\cdot10^4$ L cm mol^{-1}; ε_{abs3}: $4.1\cdot10^4$ L cm mol^{-1}; λ_{em}(exc 495 nm): 590 nm; Stokes shift: 86 nm; $E_{0,0}$: 2.22 eV; Cyclic voltammetry (in MeCN, vs SCE): $E_{1/2}$(P*/P$^-$): +1.36 V; $E_{1/2}$(P/P$^-$): −0.86 V.

(12) **(±)-3-(Dimethylamino)-9-(4-fluoronaphthalen-1-yl)-1,8-dimethoxy-10-phenylacridinium bromide salt (4b):** Prepared according to the above general procedures using 5-methoxy-N^1-(3-methoxyphenyl)-N^3,N^3-dimethyl-*N*-phenylbenzene-1,3-diamine (55.8 mg, 160 µmol) and methyl 4-fluoro-1-naphthoate (20.4 mg, 100 µmol). Purification gave a brown red solid (20.1 mg, 34%, HPLC purity: 93% at 400 nm, decomp. at 134 °C): R_f 0.14 (CH_2Cl_2:MeOH 10:1); ν_{max} (neat): 2934w, 1623s, 1598s, 1503s, 1469s, 1429m, 1348m, 1256s, 1233m, 1166w, 1098s, 1036w,

907w, 767s, 707m; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 8.22 (1H, d, ^3J 8.8, C5'*H*), 7.87–7.91 (2H, m, C3"*H*, C5"*H*), 7.78–7.81 (1H, m, C4"*H*), 7.55–7.61 (2H, m, C6'*H*, C6*H*), 7.46–7.52 (2H, m, C2"*H*, C6"*H*), 7.43–7.44 (2H, m, C7'*H*, C8'*H*), 7.17–7.21 (1H, m, C3'*H*), 7.01–7.04 (1H, m, C2'*H*), 6.64 (1H, d, ^3J 7.9, C7*H*), 6.57 (1H, d, ^3J 8.8, C5*H*), 6.36 (1H, d, ^4J 1.2, C2*H*), 5.48 (1H, d, ^4J 1.2, C4*H*), 3.20 (3H, s, C1OC*H*$_3$), 3.12 (6H, br, N(C*H*$_3$)$_2$), 3.04 (3H, s, C8OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 160.9 (*C1*), 159.6 (*C8*), 158.0 (d, $^2J_{CF}$ 251, C4'), 157.3 (*C3*), 154.0 (*C9*), 145.3 (*C4a*), 142.1 (*C10a*), 138.7 (*C1"*), 136.3 (*C6*), 135.9 (d, $^4J_{CF}$ 4.8, C1'), 133.5 (d, $^3J_{CF}$ 4.7, C8'a), 132.2 (*C3"*), 132.0 (*C5"*), 131.1 (*C4"*), 128.1 (*C2"*), 128.0 (*C6"*), 127.1 (*C7'*), 126.0 (*C6'*), 125.2 (d, $^4J_{CF}$ 2.6, C8'), 122.6 (d, $^2J_{CF}$ 17.0, C4'a), 121.6 (d, $^3J_{CF}$ 8.2, C2'), 120.6 (d, $^3J_{CF}$ 5.1, C5'), 116.8 (*C9a*), 115.3 (*C8a*), 109.8 (*C5*), 108.5 (d, $^2J_{CF}$ 20.4, C3'), 105.9 (*C7*), 96.2 (*C2*), 89.2 (*C4*), 56.9 (C8O*C*H$_3$), 56.2 (C1O*C*H$_3$), 41.0 (N(*C*H$_3$)$_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ= –124.6; ESI-MS: m/z calcd. for $C_{33}H_{28}FN_2O_2^+$ 503.2128 found 503.2129 [M$^+$]. Luminescence spectroscopy (in MeCN): λ_{abs1}: 501 nm; λ_{abs2}: 430 nm; λ_{abs3}: 311 nm; ε_{abs1}: 5.9·10^3 L cm mol^{-1}; ε_{abs2}: 1.0·10^4 L cm mol^{-1}; ε_{abs3}: 2.9·10^4 L cm mol^{-1}; λ_{em}(exc 496 nm): 591 nm; Stokes shift: 90 nm; $E_{0,0}$: 2.22 eV; Cyclic voltammetry (in MeCN, vs SCE): $E_{1/2}$(P*/P$^-$): +1.37 V; $E_{1/2}$(P/P$^-$): –0.85 V.

(13) **General Preparation of the *leuco*-form:** A solution of dye **4a** or **4b** in EtOH (10.0 µmol, ~0.01 molL^{-1}) was treated with a suspension of sodium borohydride in EtOH (~0.2 molL^{-1}) until the intense red color faded. The solution was concentrated *in vacuo*, extracted with Et_2O (3 x 10 mL) and washed with water (20 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give the *leuco*-form **5a** and **5b**, respectively: Guin, J.; Besnard, C.; Lacour, J. *Org. Lett.* **2010**, *8*, 1748–1751.

(14) **1,8-Dimethoxy-*N*,*N*-dimethyl-9-(naphthalen-1-yl)-10-phenyl-9,10-dihydroacridin-3-amine (5a):**
Prepared according to the above general procedure. R_f 0.62 (CH_2Cl_2 100%); ν_{max} (neat): 3361w, 3194w, 2922s, 2853m, 1632w, 1592m, 1468m, 1258m 1090m, 1021m, 909w, 798s, 733m, 700m; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 8.98 (1H, d, ^3J 8.7, C8'*H*), 7.75 (1H, d, ^3J 8.0, C5'*H*), 7.69 (1H, dd, ^3J 7.3, ^4J 0.7, C2'*H*), 7.63–7.66 (2H, m, C3"*H*, C5"*H*), 7.55–7.58 (2H, m, C4'*H*, C7'*H*), 7.48–7.52 (3H, m, C2"*H*, C4"*H*, C6"*H*), 7.41–7.44 (1H, m, C6'*H*), 7.27–7.30 (1H, m, C3'*H*), 6.82–6.85 (1H, m, C6*H*), 6.61 (1H, s, C9*H*), 6.25 (1H, d, ^3J 8.0, C7*H*), 5.92 (1H, d, ^3J 8.4, C5*H*), 5.74 (1H, d, ^4J 2.2, C2*H*), 5.28 (1H, d, ^4J 2.2, C4*H*), 3.43 (3H, s, C8OC*H*$_3$), 3.43 (3H, s, C1OC*H*$_3$), 2.66 (6H, s, N(C*H*$_3$)$_2$); see Ref 17; ^{13}C NMR (151 MHz, $CDCl_3$) δ= 158.4 (*C1*), 157.6 (*C8*), 149.9 (*C3*), 147.1 (*C1'*), 142.6 (*C10a*), 142.6 (*C4a*), 141.8 (*C1"*), 133.2 (*C4'a*), 131.4 (*C2"*, *C6"*), 131.1 (*C8'a*), 130.5 (*C3"*, *C5"*), 128.1 (*C4"*), 127.8 (*C5'*), 127.2 (*C2'*), 126.5 (*C6*), 126.1 (*C8'*), 126.0 (*C3'*), 125.7 (*C4'*), 124.6 (*C6'*), 124.3 (*C7'*), 115.7 (*C8a*), 107.7 (*C5*), 105.1 (*C9a*), 102.6 (*C7*), 92.8 (*C4*), 89.7 (*C2*), 55.2 (C1O*C*H$_3$), 55.1 (C8O*C*H$_3$), 40.5 (N(*C*H$_3$)$_2$), 30.2 (C9); ESI-MS: m/z calcd. for $C_{33}H_{31}N_2O_2^+$ 487.2380 found 487.2376 [M+H$^+$].

(15) **9-(4-Fluoronaphthalen-1-yl)-1,8-dimethoxy-*N*,*N*-dimethyl-10-phenyl-9,10-dihydroacridin-3-amine (5b):**
Prepared according to the above general procedure. R_f 0.74 (CH_2Cl_2 100%); ν_{max} (neat): 2926s, 1610s, 1468s, 1311w, 1249s, 1091m, 909w; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 8.96 (1H, d, ^3J 8.8, C8'*H*), 8.04 (1H, d, ^3J 8.4, C5'*H*), 7.61–7.66 (3H, m, C7'*H*, C3''*H*, C5''*H*), 7.57–7.60 (1H, m, C2'*H*), 7.49–7.53 (2H, m, C6'*H*, C4"*H*), 7.46–7.47 (2H, m, C2"*H*, C6"*H*), 6.94–6.98 (1H, m, C3'*H*), 6.83–6.86 (1H, m, C6*H*), 6.53 (1H, s, C9*H*), 6.25 (1H, d, ^3J 8.0, C7*H*), 5.91 (1H, d, ^3J 8.3, C5*H*), 5.74 (1H, d, ^4J 2.2, C2*H*), 5.27 (1H, d, ^4J 2.2, C4*H*), 3.44 (3H, s, C1OC*H*$_3$), 3.43 (3H, s, C8OC*H*$_3$), 2.67 (6H, s, N(C*H*$_3$)$_2$); see Ref 17; ^{13}C NMR (125 MHz, $CDCl_3$) δ= 158.3 (*C1*), 157.5 (*C8*), 156.8 (d, $^1J_{CF}$ 247, *C4'*), 149.9 (*C3*), 143.1 (d, $^4J_{CF}$ 4.5, *C1'*), 142.6 (*C10a*), 142.5 (*C4a*), 141.7 (*C1"*), 132.1 (d, $^3J_{CF}$ 4.1, *C8'a*), 131.4 (*C2"*, *C6"*), 130.5 (*C3"*, *C5"*), 128.1 (*C4"*), 126.7 (d, $^3J_{CF}$ 8.4, *C2'*), 126.6 (*C6*), 126.1 (d, $^4J_{CF}$ 2.4, *C8'*), 125.5 (*C7'*), 124.9 (d, $^4J_{CF}$ 1.3, *C6'*), 122.8 (d, $^2J_{CF}$ 15.4, *C4'a*), 119.9 (d, $^3J_{CF}$ 6.3, *C5'*), 115.4 (*C8a*), 109.6 (d, $^3J_{CF}$ 19.5, *C3'*), 107.7 (*C5*), 104.8 (*C9a*), 102.6 (*C7*), 92.7 (C4), 89.6 (*C2*), 55.1 (*C8*OCH$_3$), 55.0 (*C1*OCH$_3$), 40.5 (N(*C*H$_3$)$_2$), 30.0 (*C9*); ^{19}F NMR (471 MHz, $CDCl_3$) δ= –126.8; ESI-MS: m/z calcd. for $C_{33}H_{30}FN_2O_2^+$ 505.2286 found 505.2293 [M+H$^+$].

(16) NOE between C9*H* of the acridinium and C8'*H* of the naphthyl group suggest the structure of the major diastereomer to be ***leuco*-4** as shown in Scheme 2.

(17) **General procedure for the oxidation of the *leuco*-form:** A solution of *leuco*-form **5a** or **5b** (5.00 µmol) in CH_2Cl_2 (2.0 mL) was treated at room temperature with an excess of chloranil and was stirred until the red color persisted. The mixture was washed with water (2.0 mL) and 1 molL^{-1} aq. HBr (2 x 1.0 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue purified by chromatography over silica gel with 100% CH_2Cl_2 and CH_2Cl_2:MeOH 100:5 to provide acridinium bromide salt **4a** and **4b**: Sakabe, M.; Asanuma, D.; Kamiya, M.; Iwatate, R. J.; Hanaoka, K.; Terai, T.; Nagano, T.; Urano, Y. *J. Am. Chem. Soc.* **2013**, *135*, 409–414.

(18) (a) λ_{abs}: 425 nm; λ_{em}: 501 nm; $E_{1/2}$(P*/P$^-$): +2.06 V, $E_{1/2}$(P/P$^-$): –0.57 V vs SCE: Tsudaka, T.; Kotani, H.; Ohkubo, K.; Nakagawa, T.; Tkachenko, N. V.; Lemmetyinen, H.; Fukuzumi, S. *Chem. Eur. J.* **2017**, *23*, 1306–1317. (b) λ_{abs}: 412 nm, λ_{em}: 550 nm; $E_{1/2}$(P*/P$^-$): +1.62 V and $E_{1/2}$(P/P$^-$): –0.84 V vs SCE: Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244–7249.

(19) (a) Aliquots treated by $NaBH_4$ allowed the measurement of change in *ee%* by HPLC over time for rate of racemization (k_{rac}), the barrier to rotation ($\Delta G^{\ddagger}_{393\,K}$) and the racemization half-life ($t_{1/2}$) determination. (b) Rickhaus, M.; Jundt, L.; Mayor, M. *Chimia* **2016**, *70*, 192–202. (c) Lotter, D.; Neuburger, M.; Rickhaus, M.; Häussinger, D.; Sparr, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2920–2923 and S34 in the supporting information.

(20) Witzig, R. M.; Lotter, D.; Fäseke, V. C.; Sparr, C. *Chem. Eur. J.* **2017**, *23*, 12960–12966.

(21) The results reported in this publication form part of a patent application: Fischer, C.; Sparr, C. Patent application filed EP 17/188,288, **2017**.