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# Selective detection of Fe(III) ions in aqueous solution with a 1,8-diacridylnaphthalene-derived fluorosensor

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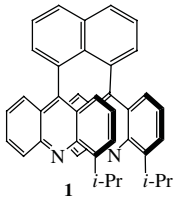
**Abstract**—The *syn*-isomer of 1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**, has been prepared by two consecutive $Pd(PPh_3)_4$-catalyzed Stille cross-coupling steps. This highly congested sensor undergoes Fe(III)-selective fluorescence quenching in water/acetonitrile even in the presence of excess of other metal ions.


Molecular probes for real-time analysis of physiologically relevant metals have recently received increasing attention. A variety of chemo and biosensors has been developed for the detection and quantification of main group and transition metals.[1] MerR-type metal regulating proteins have been used to construct biosensors for selective detection of $d^{10}$-metal ions such as $Hg^{2+}$, $Cu^{+}$, $Ag^{+}$, and $Au^{+}$.[2] The introduction of a fluorophore in close proximity to a metal-binding site has resulted in a variety of fluorosensors, albeit high metal ion selectivity in aqueous solutions has rarely been accomplished. Because of its high luminescence intensity the boron-dipyrromethene group has been combined with various ionophoric moieties, for example, 8-hydroxyquinoline for highly $Hg^{2+}$-selective sensing in dioxane–water solutions.[3] A water-soluble fluorescent naphthalimide photo-induced electron transfer sensor exhibiting an iminodiacetate receptor with high selectivity for $Zn^{2+}$ has also been reported.[4]

Following a strategy previously developed in our laboratories for the synthesis of highly congested fluorescent 1,8-dipyridylnaphthalenes,[5] diquinolylnaphthalenes,[6] and 1,8-diacridylnaphthalenes,[7] we have prepared *syn*-1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**, via Stille cross-coupling of 4-isopropyl-9-trimethylstannylacridine, **2**, and dibromonaphthalene, **3**. Herein, we wish to present an improved synthetic procedure toward **1**, its single crystal structure, and its use as a highly selective fluorosensor for Fe(III) ions in aqueous solution (Fig. 1).

1,8-Disubstituted naphthalenes have received increasing attention because of their unique stereochemical and electronic properties. For example, a blue-transparent frequency-doubling device using 1,8-dihetarylnaphthalenes exhibiting nonlinear optical effects[8] and a 1,8-diarylnaphthalene-derived bis(manganese) complex with water splitting activity upon irradiation of visible light have been developed.[9] The introduction of bulky substituents into the *peri* positions of naphthalene is difficult to achieve because of the considerable steric hindrance that impedes formation of such a highly constrained framework.[10] In particular, the formation of 1,8-diacridylnaphthalenes by Stille cross-coupling of 1,8-dihalonaphthalenes and 9-acridylstannanes is severely hindered because of the steric repulsion between the *peri* acridyl rings. Screening of various Pd catalysts and reaction conditions revealed that 1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**, can be prepared in 30%



**1**

**Figure 1.** Structure of *syn*-1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**.

*Keywords*: Stille coupling; Congested aromatic compounds; 1,8-Diacridylnaphthalenes; Fluorosensing; Metal ions.
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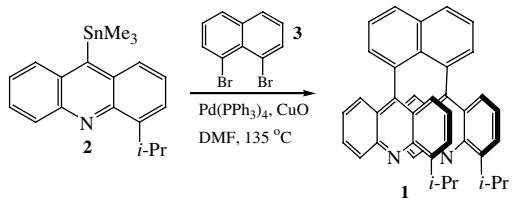
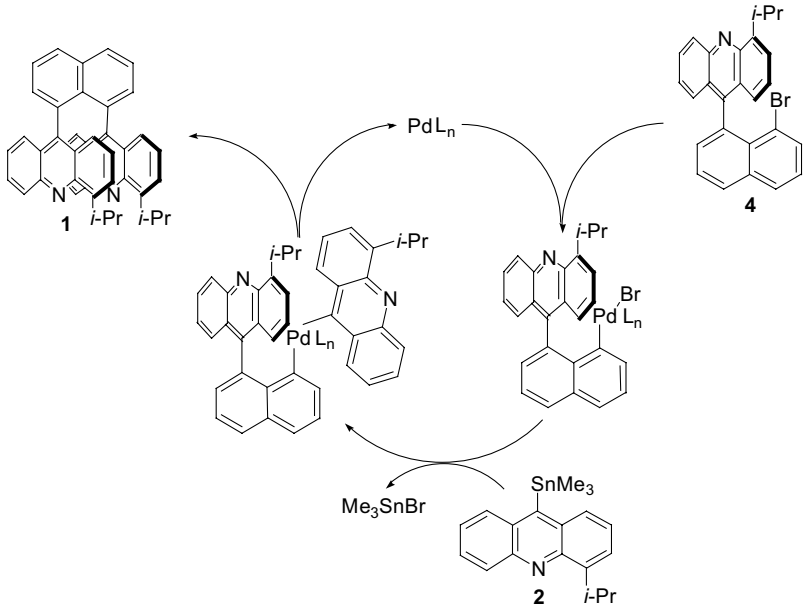



**Scheme 1.** Synthesis of *syn*-1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**, by Stille coupling of 4-isopropyl-9-trimethylstannylacridine, **2**, and dibromonaphthalene, **3**.

yield by CuO-promoted $Pd(PPh_3)_4$-catalyzed Stille cross-coupling of 4-isopropyl-9-trimethylstannylacridine, **2**, and dibromonaphthalene, **3** (Scheme 1).[11]

The synthesis of **1** requires two consecutive Stille coupling reactions that involve sterically crowded Pd complexes, in particular during the Pd-catalyzed reaction between the intermediate 1-bromo-8-(4-isopropylacridyl)naphthalene, **4**, and a second equivalent of stannane **2** (Scheme 2). During the first and presumably less hindered coupling step, acridylstannane **2** and dibromide **3** yield bromide **4**, which enters another Pd-catalyzed coupling cycle. The formation of diacridylnaphthalene **1** is accomplished by oxidative addition of bromide **4** to the Pd(0) catalyst followed by transmetalation with stannane **2** to afford Pd complex **5**, which gives 1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene after reductive elimination.[12] The overall yield of **1** is remarkably high considering the steric repulsion during the two catalytic steps and the strain inherent to congested diacridylnaphthalenes.

In order to determine the coordination sphere and ability to interact with Lewis acids we attempted to grow a single crystal of **1** using isothermal diffusion and evaporation methods. We were able to prepare a single crystal of **1** suitable for crystallographic analysis through slow evaporation of a methylene chloride solution.[13] Interestingly, diacridylnaphthalene **1** forms a monoclinic crystal belonging to the chiral *P*2(1) space group.[14] The chirality in the solid state arises from a locked asymmetric conformation of **1** (Fig. 2).




**Scheme 2.** Illustration of the second Stille coupling step between 1-bromo-8-(4-isopropylacridyl)naphthalene, **4**, and stannane **2**.

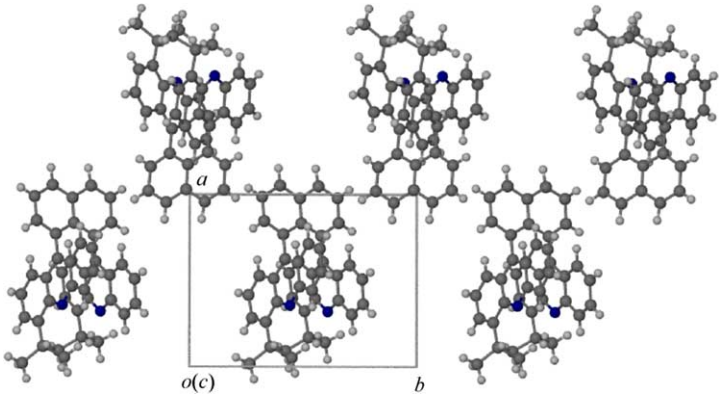



**Figure 2.** Chiral packing arrangement of **1**.

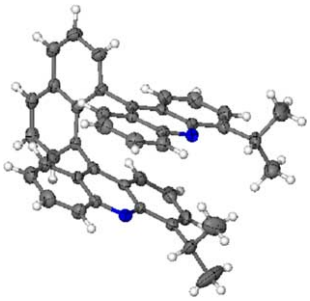


**Figure 3.** Spatial arrangement of the parallel 4-isopropylacridyl rings of sensor **1**.

As expected, the close proximity of the parallel acridyl rings results in a highly congested structure (Fig. 3). To minimize steric interactions, Coulomb repulsion, and dipole–dipole interactions the two acridyl groups are slightly twisted and splayed away from each other. The torsion angle between the two acridyl ring is 21.8° and the splaying between the acridine planes was determined as 6.6°. The twisting and splaying between the 4-isopropylacridyl moieties results in an *N–N* distance of 4.027 Å (Table 1). The X-ray analysis shows that **1** forms a cleft into which metal ions can diffuse to interact with the acridyl nitrogen atoms. However, the close proximity of the isopropyl groups partially shields the nitrogen atoms and restricts coordination of ligand **1** to metal ions of appropriate size. The spatial arrangement of the parallel 4-isopropylacridyl rings thus creates a rigid and well-defined binding environment for metal ion-selective recognition.

We employed **1** in fluorescence experiments using a variety of metal chlorides in water/acetonitrile (1:1, v/v). Fluorescence studies of **1** revealed a quantum yield of 18% and an emission maximum of 550 nm that did not shift in the presence of metal ions (Fig. 4).[15] We expected that coordination of the diacridylnaphthalene sensor to transition metal ions exhibiting unoccupied d-orbitals would result in considerable fluorescence quenching because of photo-induced electron transfer. The screening of various main group and transition

**Table 1.** Selected crystallographic data of **1**

| | |
|---|---|
| Empirical formula | $C_{42}H_{34}N_2$ |
| Formula weight | 566.71 |
| Crystal system | Monoclinic |
| Space group | *P*2(1) |
| Unit cell dimensions | $a = 10.664(6)$ Å |
| | $b = 12.755(7)$ Å |
| | $c = 12.040(6)$ Å |
| | $\alpha = 90°$ |
| | $\beta = 114.923(19)°$ |
| | $\gamma = 90°$ |
| Volume | 1485.2(13) Å$^3$ |
| *Z* | 2 |
| Density (calculated) | 1.267 mg/m$^3$ |
| Crystal size | $0.5 \times 0.5 \times 0.2$ mm$^3$ |
| *N–N* distance | 4.027 Å |
| Torsion between the acridyl rings | 21.8° |
| Splaying between the acridyl rings | 6.6° |

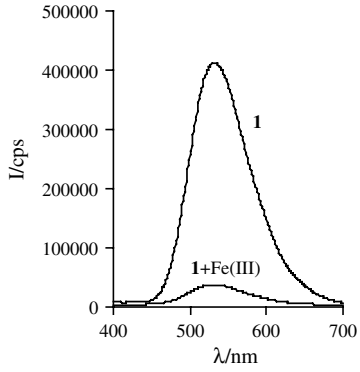



**Figure 4.** Fluorescence spectrum of **1** in acetonitrile/water (v/v 1:1). The concentration of **1** was $5 \times 10^{-7}$ M. The concentration of Fe(III) was $2.5 \times 10^{-5}$ M. Excitation wavelength: 360 nm.

metal chlorides showed strong fluorescence quenching by $FeCl_3$ and to some extent by Cr(II), whereas the addition of other metal salts to a solution of **1** had negligible effects on the fluorescence of the sensor (Fig. 5). Addition of 50 equiv of $FeCl_3$ to a $5 \times 10^{-7}$ M solution of **1** reduced the fluorescence intensity to 5%. The presence of main group and $d^{10}$-transition metal ions such as Cu(I), Zn(II), Cd(II), and Hg(II) did not result in any fluorescence quenching, which is probably a consequence of negligible photo-induced electron transfer pathways for nonradiative relaxation. The absence of significant fluorescence quenching effects by Mn(II), Ni(II), Fe(II), and Cu(II) in aqueous solutions renders **1** a highly useful Fe(III)-selective sensor. It should be noted that diacridylnaphthalene **1** can also be used to differentiate between the oxidation states of iron. Moreover, excellent selectivity of the sensor for Fe(III) in the presence of $3.5 \times 10^{-5}$ M of Mn(II), Cu(II), and Zn(II) chlorides was observed (Fig. 5).

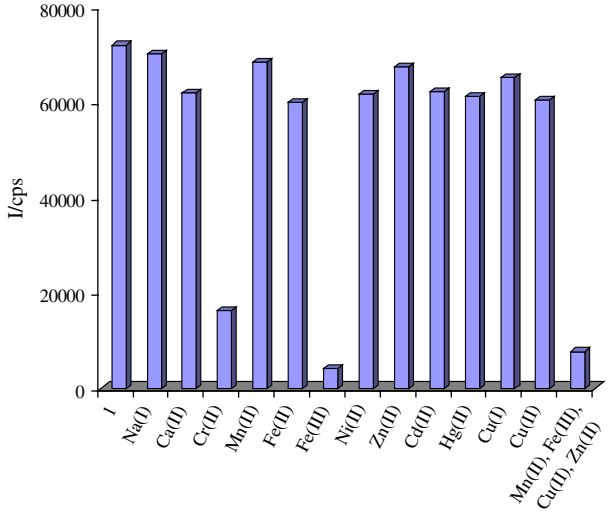



**Figure 5.** Fluorescence of **1** in acetonitrile/water (v/v 1:1) in the absence and presence of metal ions. The concentration of **1** was $7 \times 10^{-7}$ M. The metal ion concentration was $3.5 \times 10^{-5}$ M. Excitation wavelength: 363 nm. Emission wavelength: 550 nm.

The highly selective quenching of 1,8-diacridylnaphthalene **1** by ferric chloride in aqueous solution may therefore be utilized for the diagnosis of iron-related diseases such as anemia and hemochromatosis. The determination of iron in blood serum and other body fluid samples is important for the study, diagnosis, and treatment of nutritional and metabolic diseases that cause low or high iron levels. Iron metabolism disorders have been found to cause iron-deficiency anemia and hemochromatosis, which might ultimately result in liver cancer, liver cirrhosis, arthritis, diabetes, or heart failure.[16] Recent studies have linked late-onset neurodegenerative disorders such as Parkinson's disease to elevated iron levels.[17] The analysis of iron levels in blood serum and cell extracts is crucial for the diagnosis and treatment of cancer because high amounts of iron are during tumor cell proliferation. Iron also plays a role in important infectious diseases such as malaria.[18]

In summary, *syn*-1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**, was prepared via CuO-promoted $Pd(PPh_3)_4$-catalyzed Stille cross-coupling of 4-isopropyl-9-trimethylstannylacridine, **2**, and dibromonaphthalene, **3**. Single crystal X-ray analysis of **1** revealed a rigid metal-ion binding pocket formed by the two slightly twisted and splayed 4-isopropylacridyl rings. Employing **1** in fluorescence studies showed highly Fe(III)-selective quenching in water/acetonitrile (1:1, v/v) even in the presence of excess of other metal ions, which makes the 1,8-diacridylnaphthalene-derived sensor attractive for trace analysis and diagnosis of iron-related diseases. Fluorescent chemosensors usually exhibit a chelating group physically separated from a fluorophore by a spacer.[19] However, smaller sensors such as *syn*-**1** may afford superior cell permeability properties and are therefore particularly interesting with respect to biomedical applications.

## Acknowledgements

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11. In our hands $Pd(PPh_3)_4$ proved to be superior over $PdCl_2$dppf or $Pd_2(dba)_3$/*t*-$Bu_3P$.
12. Preparation of *syn*-1,8-bis(4,4′-diisopropyl-9,9′-diacridyl)naphthalene, **1**. A mixture of 4-isopropyl-9-trimethylstannyl acridine **2** (1.45 g, 3.8 mmol), 1,8-dibromonaphthalene **3** (0.25 g, 0.89 mmol), $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol, 20 mol%), and CuO (0.1 g, 1.27 mmol) in 20 mL DMF was refluxed overnight under nitrogen. The reaction mixture was quenched with 10% aqueous ammonium hydroxide and extracted with diethyl ether. Evaporation of the solvent under reduced pressure gave a residue that was purified by flash chromatography on silica gel using 100:5:1 hexanes/ethyl acetate/triethylamine as the mobile phase to afford an equimolar mixture of *syn*- and *anti*-**1** (150 mg, 30%) as a yellow solid. The *syn*-isomer was isolated by HPLC using a phenylglycine column (250 mm × 4.6 mm) and hexanes/EtOH (98.8:1.2) as the mobile phase. $^1$H NMR: $\delta$ = 1.22 (d, $J$ = 6.9 Hz, 6H), 1.52 (d, $J$ = 6.9 Hz, 6H), 4.23 (sept, $J$ = 6.9 Hz, 2H), 6.59–6.78 (m, 6H), 7.20–7.37 (m, 8H), 7.64–7.72 (m, 4H), 8.26 (dd, $J$ = 1.6 Hz, $J$ = 8.4 Hz, 2H). $^{13}$C NMR: $\delta$ = 24.62, 26.98, 27.08, 123.54, 123.95, 124.60, 124.71, 125.16, 125.52, 125.74, 128.09, 129.69, 129.93, 130.79, 134.59, 134.70, 144.95, 145.01, 145.57, 145.77, 146.79. Anal. Calcd for $C_{42}H_{34}N_2$: C, 89.01; H, 6.05; N, 4.94. Found: C, 89.38; H, 6.25; N, 4.67.
13. A single crystal of **1** was obtained through slow evaporation of a methylene chloride solution of the chromatographically purified *syn*-isomer at room temperature

single crystal X-ray diffractions were collected at −100 °C using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined with full-matrix least-squares/difference Fourier analysis using SHELX-97-2 software. Nonhydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were placed in calculated positions and refined with a riding model. Data were corrected for the affects of absorption using SADABS.

14. Crystallographic data for **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236847. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Fax: 44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
15. The quantum yield of **1** was determined using degassed solutions following a procedure described by Jones and co-workers. The sensor was excited at 360 nm and the integrated intensity of the emission spectrum was compared to naphthalene, which has a quantum yield of 0.2 in acetonitrile. Jones, G., II; Jackson, W. R.; Choi, C.-Y. *J. Phys. Chem.* **1985**, *89*, 294–300.
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