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Determination of enantiomeric excess and concentration of chiral compounds using a 1,8-diheteroarylnaphthalene-derived fluorosensor

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Abstract—Enantioselective fluorosensing using a rigid C_2-symmetric 1,8-diacridylnaphthalene N,N'-dioxide sensor allows accurate determination of both the enantiomeric composition and concentration of several analytes capable of chiral hydrogen bonding.

The development of enantioselective fluorescence assays suitable to high-throughput screening of asymmetric reactions has recently received increasing attention.[1] Fluorescence spectroscopy combines several attractive features such as different detection modes (fluorescence quenching, enhancement, and lifetime measurements), high sensitivity, low cost of instrumentation, waste reduction, and time-efficiency.[2] The potential use of fluorescence sensing for rapid determination of the enantioselectivity of asymmetric reactions has been demonstrated with the titanium tartrate-catalyzed silylcyanation of an immobilized aldehyde and the kinetic resolution of *trans*-1,2-diaminocyclohexane using *Candida Antarctica*.[3] In both cases, fluorescence measurements provided accurate ee's and proved superior over laborious and time-consuming chromatographic methods. We have developed a synthetic entry to highly congested 1,8-diquinolyl- and 1,8-diacridylnaphthalenes and shown the use of this class of compounds for enantioselective recognition of chiral hydrogen bond donors. The unique geometry and rigid structure of C_2-symmetric 1,8-diheteroarylnaphthalenes and their N,N'-dioxides result in a well-defined chiral cleft that places hydrogen bond interactions into a highly stereoselective environment. Previous X-ray and NMR spectroscopic studies conducted in our laboratories have shown that 1,8-diheteroarylnaphthalenes are highly congested, rigid structures that possess remarkable one-dimensional flexibility.[4] The two cofacial heteroaryl rings reside perpendicular to the naphthalene ring and undergo little splaying. However, the torsional angle, τ, can change over a range of 50°, in particular upon binding to a hydrogen bond donor (Fig. 1).[5] We believe that this one-dimensional conformational flexibility facilitates accommodation of substrates of varying size in the C_2-symmetric pocket of these fluorescent probes. Herein, we report the usefulness of 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene N,N'-dioxide, **1**, for the

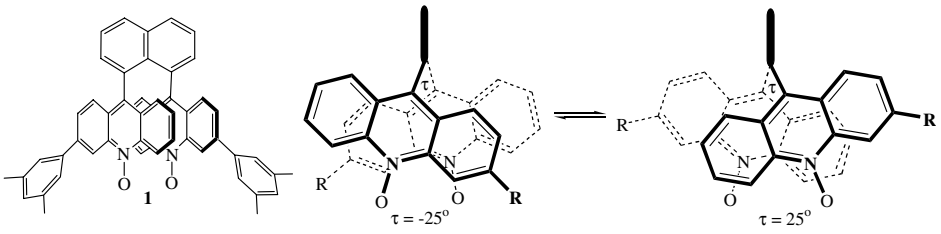

Figure 1. Structure of **1** and one-dimensional flexibility of 1,8-diheteroarylnaphthalenes.

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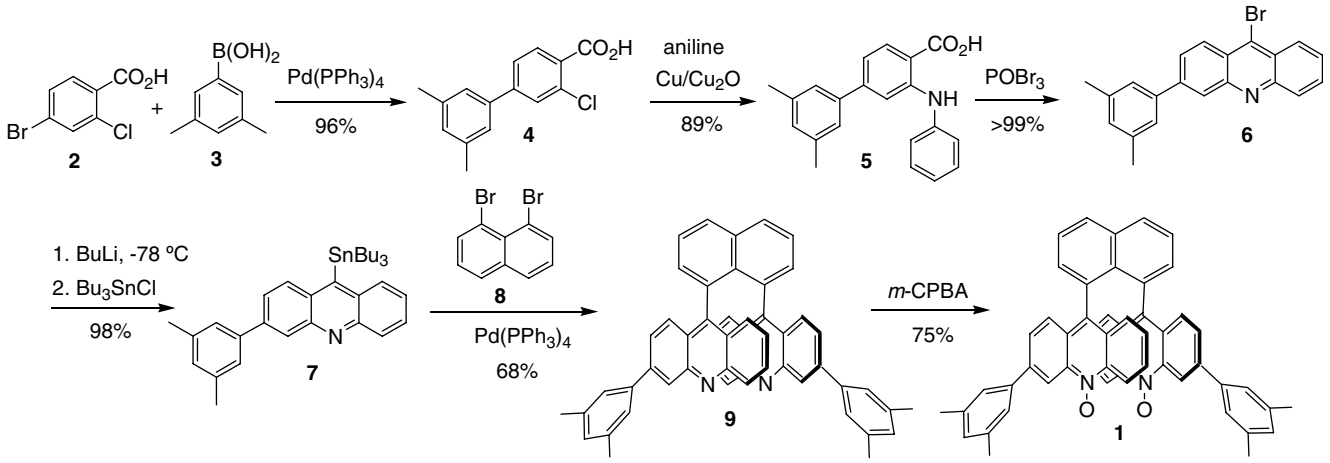

Scheme 1. Synthesis of 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene *N*,*N*′-dioxide **1**.

determination of both enantiomeric excess and concentration of several chiral compounds.

The synthesis of 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene *N*,*N*′-dioxide, **1**, involves Suzuki coupling of 4-bromo-2-chlorobenzoic acid, **2**, and 3,5-dimethylphenylboronic acid, **3**, to afford biaryl **4** in almost quantitative amounts, Scheme 1. Copper-catalyzed amination of **4** using a procedure previously reported from our laboratories followed by ring closure of anthranilic acid **5** with phosphorus oxybromide gives 9-bromoacridine **6** in excellent yields.[6] Lithiation and subsequent stannylation of **6** using tributylstannyl chloride yields stannane **7**, which is then employed in $Pd(PPh_3)_4$-catalyzed Stille coupling with 1,8-dibromonaphthalene to afford 1,8-diacridylnaphthalene **9**. The corresponding *N*,*N*′-dioxide **1** is then obtained by oxidation with *m*-chloroperbenzoic acid.

1,8-Diacridylnaphthalene *N*,*N*′-dioxide **1** is fluorescent with an emission maximum at 571 nm (excitation wavelength: 490 nm). In order to reveal the usefulness of **1** for enantioselective sensing we employed chiral analytes **10**–**15** in fluorescence titration experiments (Fig. 2).

We were pleased to find that micromolar concentrations of (+)-**1** suffice for differentiation of the enantiomers of all substrates tested (Fig. 3). Titration experiments with *t*-Boc-protected valine showed more effective quenching of the fluorescence of (+)-**1** when the (*S*)-enantiomer of

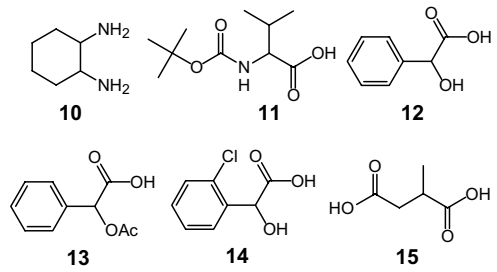

Figure 2. Analytes employed in enantioselective sensing studies with **1**.

11 was used. However, when (−)-**1** was employed in the same titration experiment, fluorescence quenching substitution occurred more readily when (*R*)-**11** was added thus proving that the observed fluorescence changes are indeed a result of enantioselective recognition and not due to impurities that could have a strong quenching effect and be present in only one of the enantiomeric analyte samples. In general, (*R*)-carboxylic acids **12**–**15** were found to be more effective fluorescence quenchers than the corresponding (*S*)-enantiomers. The enantiomers of diamine **10** selectively enhance the fluorescence intensity of **1**. The fluorescence enhancement observed in the presence of diaminocyclohexane **10** may be a consequence of increased rigidity of **1** upon complexation to **10** while enantioselective fluorescence quenching of excited *N*,*N*′-dioxide **1** by acids **11**–**15** may be attributed to quenching via non-radiative relaxation of diastereomeric hydrogen-bond adducts. While all analytes show linear Stern–Volmer plots indicating formation of equimolar diastereomeric hydrogen-bond adducts, we obtained a non-linear relationship with 2-chloromandelic acid **14**, which can be attributed to both static and dynamic quenching interactions.[5c]

We then decided to develop a fluorescence method that allows accurate measurements of both the total amount and the enantiomeric composition of chiral compounds. We found that this can be accomplished by combination of two assays. We observed that addition of either enantiomer of substrate **13** to a solution of the racemic sensor gives superimposable fluorescence titration curves. We therefore expected that the total concentration of a chiral substrate can be determined by fluorescence sensing using racemic *N*,*N*′-dioxide **1** while employment of the enantiopure sensor in literally the same fluorescence titration experiment would allow analysis of the enantiomeric composition. Six samples of **13** exhibiting different concentrations and enantiopurities ranging from 10% to 95% were prepared and subjected to fluorescence analysis. First, the fluorescence signal of the racemic sensor in the presence of each sample was measured and compared to a calibration curve for determination of the individual concentrations (Table 1). Having deter-

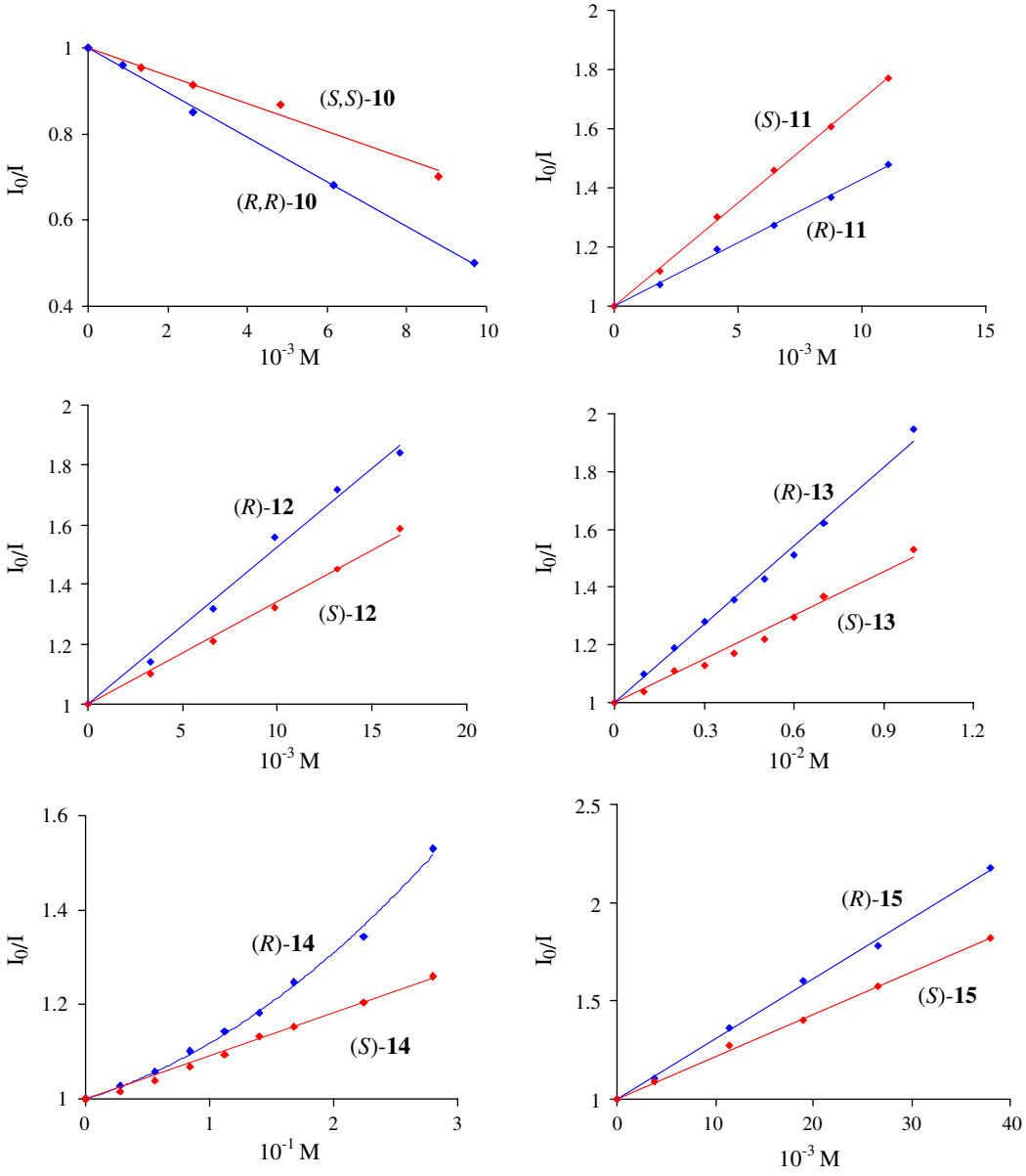

Figure 3. Stern–Volmer plots of 3.5×10^{-5} M of (+)-**1** in the presence of the enantiomers of analytes **12**–**15** in acetonitrile. Excitation wavelength: 490 nm; emission wavelength: 571 nm.

Table 1. Concentration and enantiomeric composition of nine samples of **13** determined by fluorosensing

Sample	Actual concn 10^{-2} [M]	Actual % (*R*)	Calcd concn 10^{-2} [M][a]	Calc. (%) (*R*)[a]
A	1.00	95	0.96	91
B	1.00	40	1.05	33
C	1.00	10	1.10	3
D	0.70	90	0.68	80
E	0.70	35	0.73	26
F	0.70	5	0.69	3

[a] Average of three fluorescence measurements at 571 nm.

mined sample concentrations, we were then able to reveal the enantiomeric composition of each sample using enantiopure (+)-**1** (Fig. 4 and Supplementary data). In all cases, results obtained by our fluorescence sensing method were in good agreement with actual amounts and enantiomeric compositions. The data demonstrate the high reproducibility and accuracy of this approach, which is applicable to the screening of samples exhibiting a wide range of enantiopurity and excess of either enantiomer.

In summary, we have prepared diacridylnaphthalene *N*,*N*′-dioxide **1** exhibiting a C_2-symmetric cleft designed for chiral recognition of hydrogen bond donors such as **10**–**15**. The use of **1** for quantitative stereoselective fluorescence analysis of both yield and enantiomeric composition of chiral compounds has been demonstrated. We have developed a practical method that first utilizes racemic *N*,*N*′-dioxide **1** and then its pure enantiomer in two facile fluorescence sensing assays. We believe that this approach combines several attractive features: it overcomes the difficulty in the determination of both

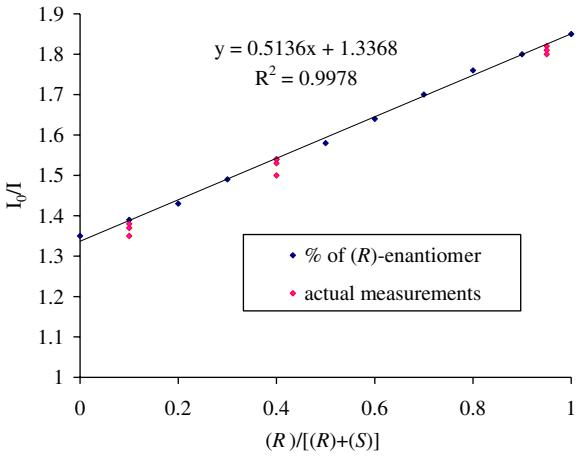

Figure 4. Fluorescence response of (+)-**1** as a function of the enantiomeric composition of **13** and determination of actual % (*R*)-**13** of three samples. The concentration of (+)-**1** was 2.50×10^{-5} M and the total concentration of **13** was 1.00×10^{-2} M in acetonitrile. Results are given in Table 1. Excitation (emission) wavelength: 490 nm (571 nm).

concentration and enantiomeric composition by the use of one sensor (in its racemic and enantiopure form), it depends on two simple assays that provide accurate values with high reproducibility, it eliminates the need for substrate derivatization, and it utilizes a cost-effective and sensitive technique (fluorescence spectroscopy) that minimizes production of solvent waste.

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Supplementary data

Synthesis and characterization of **1** and actual measurements of the concentration and enantiopurity of several samples. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.012.

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