# Fluorescence Redox Switches Based on the Opening and Closing of an Oxazabicyclic Ring

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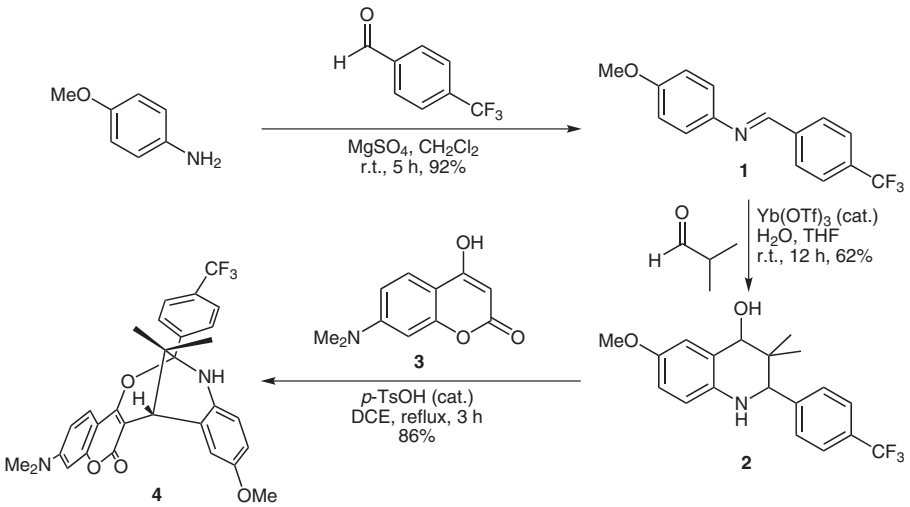
**Abstract:** A reversible donor–acceptor fluorescence redox switch connected by a rigid but redox-adjustable spacer that can be chemically turned ON and OFF through the ring opening and ring closing of a heterobicyclic moiety is demonstrated. A coumarin-based oxazabicyclic derivative was efficiently synthesized as an example for illustration. While the rigid ring-closed oxazabicycle emits moderate fluorescence in toluene, the sodium borohydride induced ring opening of the heterobicyclic moiety results in a distinct decrease in fluorescence. The resulting nonfluorescence ring-opened form can be reverted to the original fluorescence ring-closed form via DDQ or $H_2O_2$ oxidation.

**Key words:** oxazabicycle, fluorescence redox switch, redox-adjustable spacer

The field of molecular switches has attracted great interest in the past few decades because of their relevance in the development of molecular electronics and photonics.[1] Particular attention is focused on molecular switches whose emission properties are regulated by redox potential since they may have a wide range of applications in this area, such as biochemical and biophysical investigations.[2] Two different types of molecular fluorescent switching systems have been reported in the literature. One contains a metal ion and the other is metal-free and all organic. The former normally consists of a metal-centered redox couple[3] or a luminescent ion core encircled by a macrocyclic receptor.[4] The fluorescence emission of the complex can be controlled by the different oxidation state of the centered metal ion. The latter comprises a fluorophore (the donor) and an active redox switch (the acceptor), which are covalently connected by a conjugated or unconjugated spacer.[5] The fluorescence emission of the donors can be reversibly quenched depending upon the oxidation state of the acceptors. Many variables may influence the electronic communication between the fluorophore and the active redox quencher. For instance, the fluorescence quenching efficiency of a donor–acceptor system is highly sensitive to the structure, length, and rigidity of the spacer.[6] Therefore, we envisioned a fluorescence redox switch with a rigid but redox-adjustable spacer may have a major influence on the quenching efficiency of the resulting donor–acceptor system. The aim of the present study is to design a fluorescence redox switch system using a structural rigid but redox-sensitive spacer to manipulate the donor–acceptor quenching efficiency and to explore how the redox-controlled ring-opening and ring-closing of a heterobicyclic skeleton may affect its switching photochemical property.

For the current study, the coumarin derivatives were chosen as the fluorophore, since they have been intensively studied for their wide applications as laser dyes, ionophores, and fluorescence markers.[7] The aromatic amines




**Scheme 1**

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were selected as the intramolecular quencher, because the fluorescence quenching of organic compounds by aromatic amines has been well documented.[8] In this particular design, the fluorophore and the quencher are connected by a rigid heterobicyclic ring. The *gem*-dimethyl groups are also introduced onto the methylene carbon of the heterocyclic moiety to prevent the possible undesired aromatization reaction after reduction. Scheme 1 describes the preparation of the designed oxazabicyclic compound **4**. It began with the $MgSO_4$-mediated condensation of *p*-anisidine and *p*-trifluoromethyl-benzaldehyde to afford the imine **1**, followed by a $Yb(OTf)_3$-catalyzed coupling with isobutyraldehyde to give the cyclic amino alcohol **2**.[9] Subsequent coupling of **2** with 4-hydroxy-7-dimethylaminocoumarin (**3**) in the presence of a catalytic amount of *p*-toluenesulfonic acid in 1,2-dichloroethane under reflux conditions yielded the cyclized target compound **4**.[10] The bond formation during the construction of the bicyclic skeleton of **4** was highly efficient, with a total mass loss of only 38 g/mol, that is, the release of two molecules of water and one molecule of hydrogen. Since the aforementioned three synthetic steps could all be acid-catalyzed, compound **4** was alternatively prepared via a multicomponent reaction (MCR),[11] as shown in Scheme 2. The oxazabicycle **4** was obtained in a one-pot tandem reaction with 67% yield by first mixing *p*-anisidine with *p*-trifluoromethylbenzaldehyde, isobutyraldehyde, and $Yb(OTf)_3$ (0.4 equiv) in 1,2-dichloroethane at room temperature for 12 hours, following by addition of **3** and subsequently refluxing for 3 hours.[12] It is noteworthy that the yield of **4** (67%) by the MCR method is much higher than the overall yield (49%) of the stepwise reactions shown in Scheme 1. In the $^1H$ NMR spectra of the synthesized **4**, a characteristic bridgehead hydrogen absorption peak for the oxazabicyclic ring was observed at $\delta = 3.67$ ppm. The heterobicyclic structure was further elucidated by X-ray crystallography. Figure 1 shows the ORTEP diagrams of the oxazabicycle **4**, which clearly revealed a rigid oxazabicyclo[3.3.1] skeleton.[13]

While the oxazabicycle **4** emitted moderate fluorescence with the quantum yield of 0.29 in toluene, instant fluorescence quenching occurred upon reaction of the heterobicycle with a reducing agent. Addition of sodium borohydride to the oxazabicycle **4** in methanol caused ring opening and subsequent imine reduction. The intrinsic

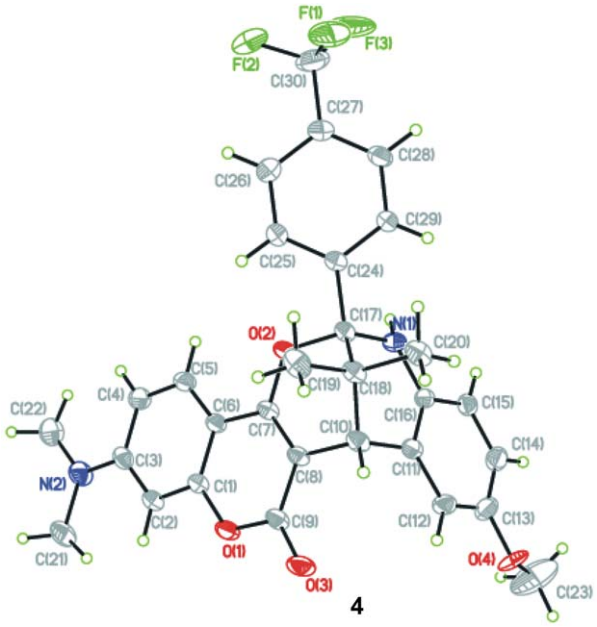
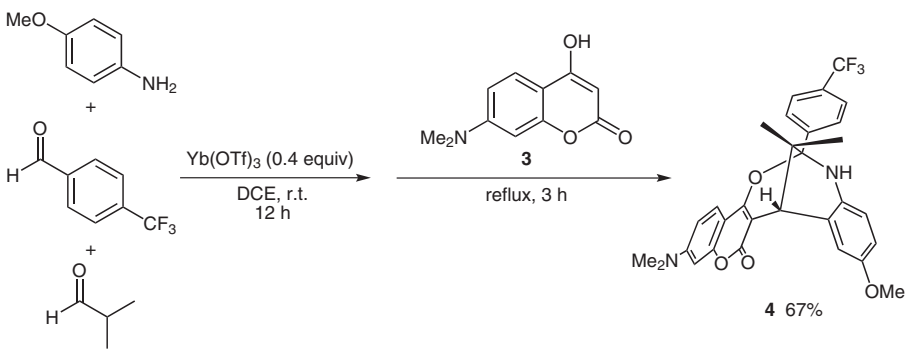



**Figure 1** X-ray crystal structure of the oxazabicycle **4**

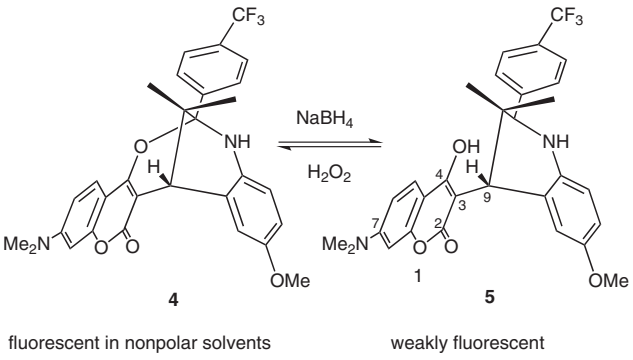
fluorescence emission of the amino alcohol **5** was found to be entirely quenched by the aromatic amine (anisidine) upon reduction. The reduction process was reversible, and the fluorescent emission of **5** could be instantly switched on via 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or $H_2O_2$ oxidation. The reversible reduction–oxidation sequence between compounds **4** and **5** was repeated more than 10 times without the observation of any detectable byproducts. Scheme 3 shows the redox switch between the ring-closed form **4** and ring-opened form **5**.

Table 1 lists the fluorescence parameters and quantum yields ($\Phi_F$) of the ring-closed oxazabicycle **4** and amino alcohol **5** in different solvents. When the coumarin fluorophore and the anisidine quencher were fixed by a rigid bicyclic ring as in the ring-closed oxazabicycle **4**, the emission of the coumarin fluorophore is partially quenched by the amine group. Also, the emission is solvent dependent, that is, the fluorescence of **4** increases as the solvent polarity decreases, presumably due to the presence of amine hydrogen atom at the anisidine moiety. After sodium borohydride mediated heterobicyclic ring opening, the bond between C-3 and C-9 in **5** (see com-




**Scheme 2**

pound **5** in Scheme 3 for atom labeling) can now freely rotate. The intrinsic fluorescence of the coumarin in the ring-opened amino alcohol **5** was found to be substantially quenched by the adjacent amine group in most of the solvents. Apparently, a more flexible conformation upon ring opening of **4** might contribute a certain role in quenching the fluorescence of **5**. This observation suggested that the donor–acceptor quenching efficiency of the fluorescence redox switch can be manipulated by a rigid but redox-adjustable heterobicyclic spacer. For easy comparison, Figure 2 shows the bar graph of the fluorescence quantum yields of **4** and **5** in different solvents. Note that the emission of both compounds is solvent-dependent, however, in contrast to compound **4**, the fluorescence of **5** increases as the solvent polarity increases, probably due to the presence of the 4-hydroxyl hydrogen atom at the coumarin moiety after reduction, which may form a hydrogen bonding between **5** and a solvent molecule in an excited singlet state.




**Scheme 3**

**Table 1** Fluorescence Parameters for Compounds **4** and **5**

| Compd | Solvent | $\lambda_{ex}$ (nm) | $\lambda_{em}$ (nm) | Stoke's shift ($cm^{-1}$) | $\Phi_F$ |
|---|---|---|---|---|---|
| **4** | MeOH | 353 | 418 | 4405 | 0.042 |
| **4** | MeCN | 352 | 406 | 3779 | 0.133 |
| **4** | $CH_2Cl_2$ | 354 | 396 | 2996 | 0.239 |
| **4** | toluene | 335 | 378 | 3396 | 0.290 |
| **5** | MeOH | 333 | 381 | 3852 | 0.052 |
| **5** | MeCN | 332 | 383 | 3874 | 0.026 |
| **5** | $CH_2Cl_2$ | 346 | 401 | 3964 | 0.017 |
| **5** | toluene | 329 | 371 | 3441 | 0.007 |

Since the oxazabicycle **4** and amino alcohol **5** can be swiftly interconverted by redox reaction, and the fluorescence intensity of the oxidized **4** in toluene is more than 40-fold stronger than that of the reduced **5**, this reversible redox process between **4** and **5** can be considered to be a molecular switch. Our studies have demonstrated the feasibility of using a structural rigid but redox-sensitive spacer to control the donor–acceptor quenching efficiency. We believe that this new molecular switching mechanism may lead to future development of the fluorescence redox switches with novel molecular structures.

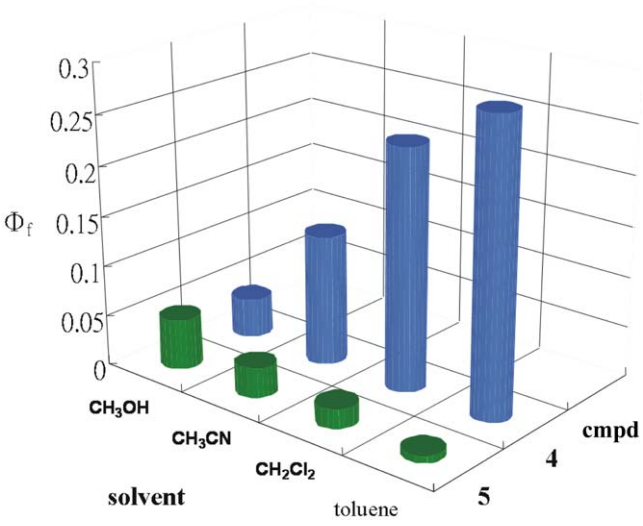



**Figure 2** Fluorescence quantum yields of **4** and **5** in different solvents

In summary, a novel oxazabicycle-based reversible fluorescence redox switch, in which the fluorophore and the quencher were connected by a rigid but redox-adjustable heterobicyclic spacer, was designed and synthesized via a stepwise reaction and by MCR. Our studies indicated that the emission of the fluorophore could be controlled by sodium borohydride induced ring opening and DDQ or $H_2O_2$-mediated ring closing of the heterobicyclic moiety. Thus, we have demonstrated that the all-organic donor–acceptor quenching efficiency can be manipulated by a redox-adjustable oxazabicyclic spacer. Investigations for the development of more sophisticated systems based on the same mechanism for colorimetric/fluorescent redox switches are in progress in our laboratory.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Procedure for the Preparation of 4**
To a solution of *p*-anisidine (1.0 mmol), 4-(trifluoromethyl)-benzaldehyde (1.0 mmol), isobutyraldehyde (1.0 mmol), and a catalytic amount of $Yb(OTf)_3$ (0.4 mmol) in DCE (10 mL) was stirred at r.t. for 12 h. 4-Hydroxy-7-dimethylamino-coumarin (1.0 mmol) was added to the mixture, and the resulting solution was refluxed for 3 h. After being cooled to r.t., the reaction was quenched with $H_2O$, and the product was extracted twice with $CH_2Cl_2$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (1:9, EtOAc–hexanes) to give a white solid in a 67% yield; mp 287–288 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.1 Hz, 2 H, ArH), 7.73 (d, *J* = 8.1 Hz, 2 H, ArH), 7.59 (d, *J* = 9.0 Hz, 1 H, ArH), 7.09 (d, *J* = 3.0 Hz, 1 H, ArH), 6.63 (dd, *J* = 8.4, 3.0 Hz, 1 H, ArH), 6.58 (dd, *J* = 8.7, 2.4 Hz, 1 H, ArH), 6.54 (d, *J* = 8.4 Hz, 1 H, ArH), 6.47 (d, *J* = 2.4 Hz, 1 H, ArH), 4.91 (s, 1 H, NH), 3.80 (s, 1 H, CH), 3.78 (s, 3 H, $OCH_3$), 3.03 [s, 6 H, $N(CH_3)_2$], 0.99 (s, 3 H, $CH_3$), 0.94 (s, 3 H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 163.0, 159.9, 154.3, 153.1, 152.9, 142.7, 132.7, 131.0 (q, $J_{CF}$ = 32.0 Hz), 129.4, 129.2, 126.1, 124.8 (q, $J_{CF}$ = 3.5 Hz), 123.9 (q, $J_{CF}$ = 270.0 Hz), 113.8, 113.5, 113.4, 108.6, 104.2, 101.2, 97.9, 95.4, 55.7, 41.8, 40.1, 33.2, 22.9, 22.1. IR (KBr): ν = 3280, 2935, 1685, 1616, 1326, 1125 $cm^{-1}$. HRMS (EI): *m/z* calcd for $C_{30}H_{27}F_3N_2O_4$: 536.1923; found: 536.1922 [$M^+$].
(13) Crystallographic data (excluding structure factors) for **4** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-744666. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.