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# Fluorescence response of TICT-active aminostilbenes to copper(II) ions: redox reaction vs ion recognition

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**Abstract** Cu(II)-selective fluorescence enhancement (**1**, **2**, and **4**) or fluorescence quenching (**3**) was observed for aminostilbenes **1–4** in acetonitrile. The fluorescence responses result from efficient Cu(II)-mediated oxidation of **1–4** that forms new fluorescent species rather than from any specific noncovalent interactions. Evidence of redox reactions includes irreversible Cu(II) titration spectra, spectroscopic observation of the radical cations, and isolation of oxidized aminostilbene dimers. These results provide a new method for synthesis of tetrasubstituted tetrahydrofurans and suggest that aminostilbenes with twisted intramolecular charge-transfer activity are potential fluorescence-enhanced Cu(II) chemodosimeters. The role of Cu(II)-mediated redox reactions should be always taken into account in mechanisms for sensing of arylamine-based Cu(II)-selective fluoroionophores.

**Keywords** Aminostilbenes · Oxidation · Twisted intramolecular charge transfer (TICT) · Chemodosimeters · Fluoroionophores

## Introduction

Because of the biological and environmental importance of Cu(II) [1, 2], much effort has been devoted to development of Cu(II)-selective fluorescent probes or chemosensors for real-time detection [3–10]. Among the different fluorescence

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This paper is dedicated to Professor Kazuhiko Mizuno on the occasion of his retirement from Osaka Prefecture University.

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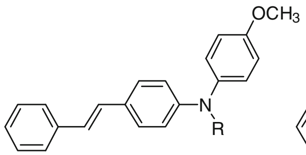
sensing modes, ion-induced fluorescence enhancement or ratiometric fluorescence responses are more useful than fluorescence quenching in terms of practical applications. However, Cu(II) is known to be an effective fluorescence quencher via excited-state energy and/or electron transfer [11]. Thus, to obtain chemosensors performing Cu(II)-induced fluorescence enhancement, the fluorescence-enhanced signaling pathways must be more efficient than the concomitant fluorescence quenching processes. Previous successful strategies include:

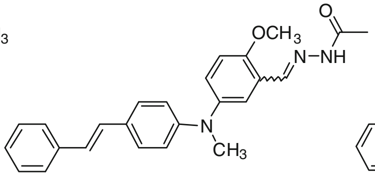
1. Cu(II)-induced inhibition of the photoinduced electron-transfer (PET) process occurring in the free fluoroionophores (i.e., PET-based probes) [3, 4];
2. Cu(II)-promoted deprotonation of donor–acceptor (D–A) type fluoroionophores that facilitates a fluorescence intramolecular charge transfer (ICT) process (i.e., ICT-based probes) [5, 6];
3. Cu(II)-induced excimer formation [7, 8]; and
4. Cu(II)-induced state inversion from a weakly fluorescent $n, \pi^*$ state to a fluorescent $\pi, \pi^*$ state [9, 10].

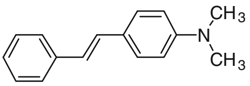
Recently, a new strategy based on the oxidizing ability of Cu(II) has emerged: namely, the fluorescent probes (chemodosimeters) are oxidized by Cu(II) and the resulting products fluoresce more strongly [12–18]. Cu(II)-mediated redox reactions are particularly effective for arylamines in organic solvents such as acetonitrile (MeCN) [19–23]. Because many Cu(II)-selective fluoroionophores reported in the literature contain arylamino moieties and have been tested in MeCN, their fluorescence sensing mechanism should be re-evaluated by considering the potential contribution of Cu(II)-mediated redox reactions.

Aminostilbenes are useful fluorophores for constructing fluorescent probes [24–26]. We have shown that in the presence of strong amino donors (e.g., those in aminostilbenes **1** and **2**) an inherently non-fluorescent or weakly fluorescent twisted intramolecular charge transfer (TICT) state is formed and its formation dominates the excited decay in polar solvents [27]. For example, the fluorescence quantum yield ($\Phi_{\mathrm{fl}}$) of **1** and **2** in hexane is high ($\Phi_{\mathrm{fl}} > 0.5$), but it becomes extremely low ($\Phi_{\mathrm{fl}} \approx 0.006$) in MeCN. The dramatic decrease in fluorescence quantum efficiency for **1** and **2** on going from nonpolar to polar solvents is a consequence of the formation of a TICT state, which is more favorable in more polar solvents [27–29]. Because TICT state formation is associated with the strong electron-donating methoxy group, modification of its electronic character by interaction with metal ions might switch off the TICT processes and thus turn on the fluorescence. Indeed, we have applied this concept to the design of a bimodal fluoroionophore (i.e., fluorescence off–on and ratiometric dual fluorescence) in response to alkaline metal ions (Mg(II), Ca(II), and Ba(II)) [25]. In an effort to further explore the Cu(II)-sensing performance of these TICT fluorophores and to investigate the relative importance of Cu(II)-mediated redox reactions and noncovalent Cu(II) recognition in the observed fluorescence responses, we have investigated the fluorescence behavior of aminostilbenes **1**–**3** and the acetylhydrazone derivatives **4**. The results reported herein show that **1**–**3** undergo efficient and selective redox reactions with Cu(II) in MeCN and the resulting fluorescence of the oxidized stilbene dimers is stronger for **1** and **2**. The redox reaction also dominates the fluorescence response of

**4** to Cu(II), despite the presence of a potential Cu(II) acceptor (i.e., *o*-methoxybenzaldehyde acetylhydrazone) [3, 10, 30]. Preparative isolation of the stilbene dimer was performed for aminostilbene **5**.







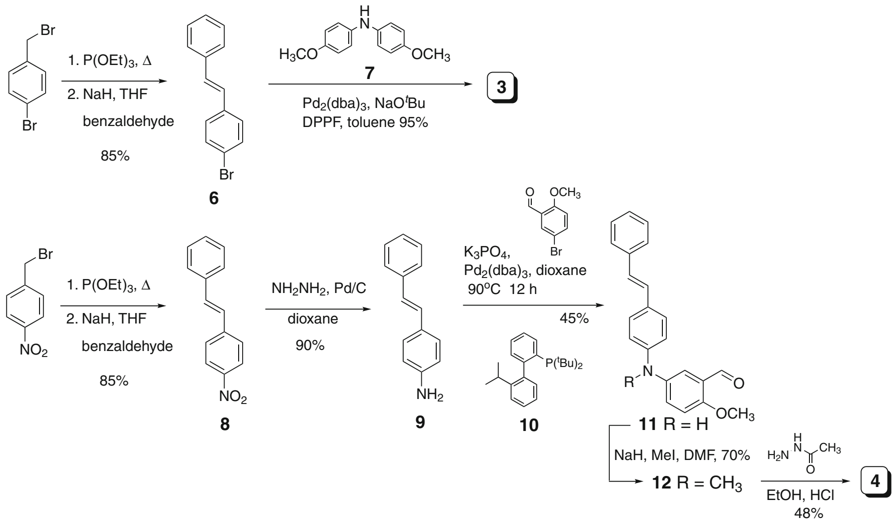
**1** R = H
**2** R = $CH_3$
**3** R = 4-$C_6H_4OCH_3$

**4**

**5**

## Results and discussion

The synthesis of aminostilbenes **1** and **2** has been reported [27]. The synthesis of **3** and **4** is shown in Scheme 1, in which intermediates **6**–**9** are all known compounds [31, 32]. The key reaction in Scheme 1 is the palladium-catalyzed C–N coupling reaction between **9** and 5-bromoanisaldehyde, which requires the phosphine ligand **10** and the base $K_3PO_4$ for success [33]. The resulting compound **11** was methylated into **12**, which was then reacted with acetic hydrazide to form the desired compound **4**. It should be noted that the product is a mixture of both trans and cis isomers in respect of the C=N bond.



**Scheme 1** Synthesis of compounds **3** and **4**

**Table 1** Maxima of UV–visible absorption ($\lambda_{abs}$) and fluorescence ($\lambda_f$), and fluorescence quantum yields ($\Phi_f$) of **1**–**4** in hexane (Hex) and acetonitrile (MeCN)

| Compd | Solvent | $\lambda_{abs}$ (nm) | $\lambda_f$ (nm) | $\Phi_f$ |
|---|---|---|---|---|
| **1**[a] | Hex | 349 | 389 | 0.60 |
| | MeCN | 356 | 502 | 0.007 |
| **2**[a] | Hex | 350 | 406 | 0.65 |
| | MeCN | 356 | 577 | 0.005 |
| **3** | Hex | 370 | 421 | 0.47 |
| | MeCN | 367 | 538 | 0.11 |
| **4** | Hex | 349 | 447 | 0.13 |
| | MeCN | 356 | 525 | 0.003 |

[a] Data from Ref. [27]

Photophysical data for **1–4** in hexane and MeCN are shown in Table 1. The absorption maxima ($\lambda_{abs}$) of aminostilbenes **1**–**4** vary only slightly on changing from hexane to MeCN. This indicates a small difference in dipole moment for the Frank–Condon (FC) excited-state vs the ground state. In contrast, both the fluorescence spectra and quantum yields ($\Phi_f$) are highly dependent on solvent polarity. The large red shift in the fluorescence spectra reflects strong ICT character in their fluorescing excited states. It is notable that in hexane the fluorescence quantum yield of **4** (0.13) is significantly lower than that of **1**–**3** (0.47–0.65), indicating that the additional hydrazone group may induce new nonradiative decay processes (e.g., C=N bond isomerization). The substantial decrease in $\Phi_f$ for **1** and **2** on going from hexane to MeCN ($\Phi_{f\text{-Hex}}/\Phi_{f\text{-MeCN}} > 86$) is a typical phenomenon of TICT state formation, and the larger the $\Phi_{f\text{-Hex}}/\Phi_{f\text{-MeCN}}$ ratio and the lower the $\Phi_{f\text{-MeCN}}$ value, the more favorable is TICT state formation in MeCN [27]. The corresponding solvent effect on $\Phi_f$ is somewhat weaker in **4** ($\Phi_{f\text{-Hex}}/\Phi_{f\text{-MeCN}} = 43$) as a consequence of the lower $\Phi_{f\text{-Hex}}$ value. In contrast, the $\Phi_{f\text{-Hex}}/\Phi_{f\text{-MeCN}}$ ratio is much lower for **3** ($\Phi_{f\text{-Hex}}/\Phi_{f\text{-MeCN}} = 4.3$) because of the larger $\Phi_{f\text{-MeCN}}$ value. It seems that introduction of the second *N*-anisolyl group, as in **3**, reduces the tendency to form a TICT state.

The ability of Cu(II) to oxidize aminostilbenes **1**–**3** in MeCN is shown by the formation of the corresponding radical cations. Figure 1 shows a parallel change in the absorption spectra of **3** on addition of Cu(II) and electrochemical oxidation. The new absorption bands (460, 533, and 733 nm) are characteristic of radical cations of triarylamines [34, 35]. In particular, the 733 nm band is close to the reported value of 737 nm for the radical cation of **4**, 4′-dimethoytriphenylamine [22]. For **1** and **2**, the absorption intensity of these peaks is rather weak, as shown in Fig. 2a for **2**. The cyclic voltammetry (CV) of **1**–**3** shows that the relative stability of their radical cations is $\mathbf{1} < \mathbf{2} < \mathbf{3}$, because reversible anodic waves are observed for **2** and **3** only at a scan rate of 100 mV/s and only that for **3** remains reversible at a scan rate as low as 5 mV/s (Fig. 3). We might conclude that oxidation of **1**–**3** is accompanied by chemical reactions with the radical cation intermediates. Indeed, addition of ethylenediaminetetraacetate (EDTA), a strong Cu(II) chelator, cannot restores the absorption bands for all cases, indicating the occurrence of an irreversible reaction between Cu(II) and aminostilbenes.

The proposed redox reaction between aminostilbenes **1**–**3** and Cu(II) (Eq. 1) is indeed thermodynamically favorable.

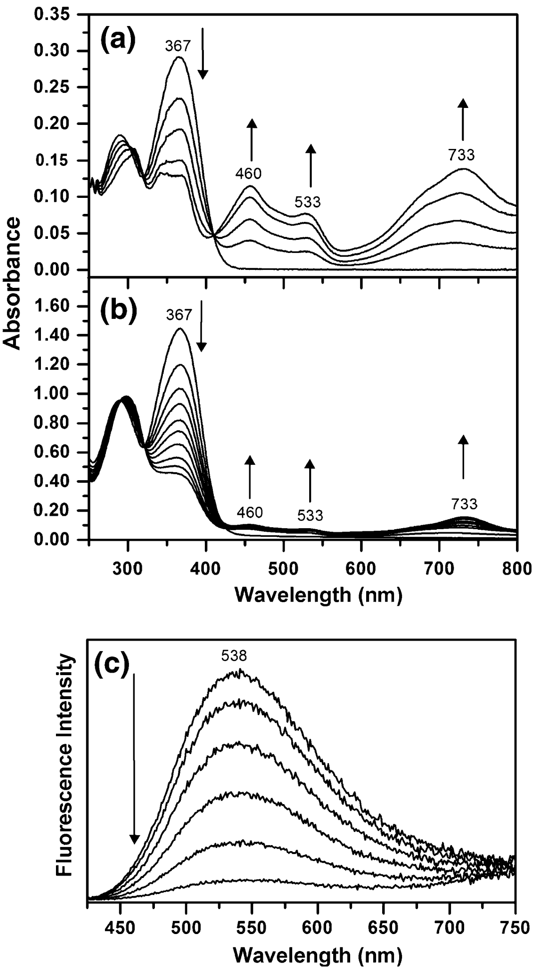


**Fig. 1** Absorption spectra of **3** in MeCN upon (**a**) addition of 0, 0.5, 1.0, 1.5, and 2.0 equiv $Cu(ClO_4)_2 \cdot 6H_2O$ and (**b**) electrochemical oxidation on a Pt electrode with $Bu_4NPF_6$ (0.1 M) as the supporting electrolyte at an applied potential of 0.6 V versus Ag wire for 0, 1, 3, 5, 10, 20, 35, 55, 75 and 120 min. (**c**) Fluorescence spectra of **3** ($1 \times 10^{-5}$ M, excitation at 405 nm) in MeCN upon addition of 0, 0.4, 0.8, 1.2, 1.6 and 2.0 equiv $Cu(ClO_4)_2 \cdot 6H_2O$

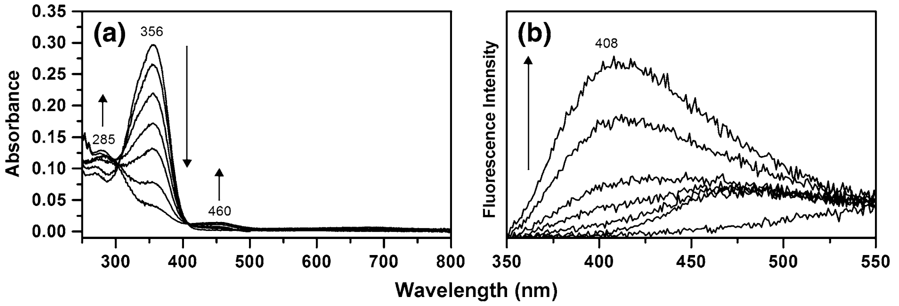


**Fig. 2** Absorption (**a**) and fluorescence (**b**) spectra of **2** ($1 \times 10^{-5}$ M, excitation at 303 nm) in MeCN upon addition of 0, 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 equiv $Cu(ClO_4)_2 \cdot 6H_2O$

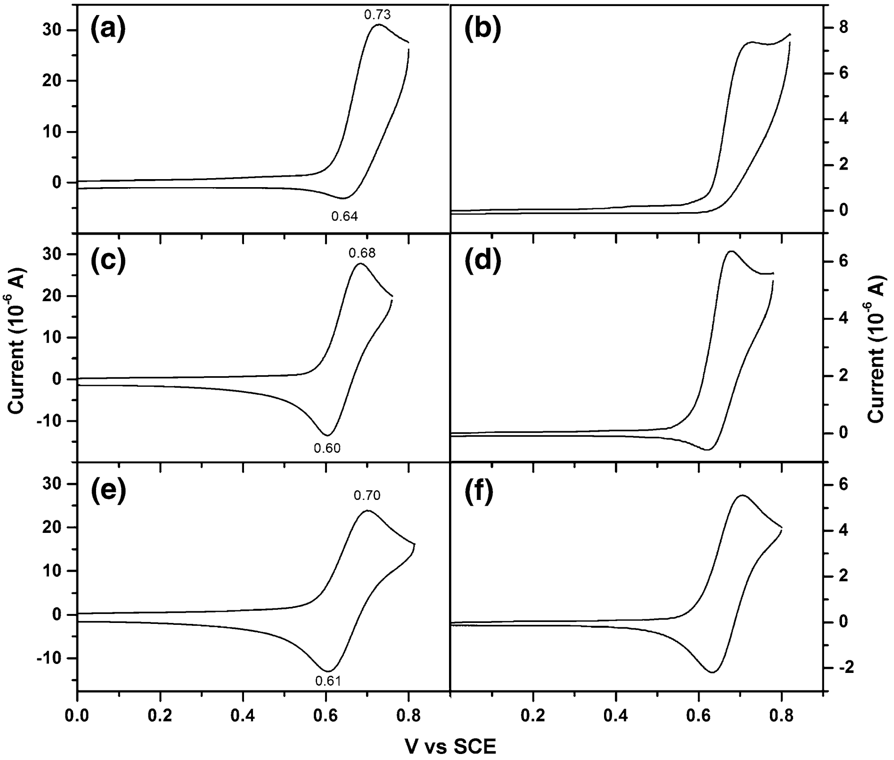


**Fig. 3** Cyclic voltammograms of **1**–**3** (1 mM) in MeCN containing 0.1 M $Bu_4NPF_6$ with a scan rate of 100 mV/s (**a**, **c**, **e**) or 5 mV/s (**b**, **d**, **f**)

$$\text{Aminostilbene} + \text{Cu(II)} \rightarrow \text{Aminostilbene}^{\cdot+} + \text{Cu(I)} \tag{1}$$

The free energy change $\Delta G$ for this electron-transfer reaction can be estimated from Eq. 2 [36–38]:

$$\Delta G = E_{\text{ox}} - E_{\text{red}} - e^2/d\varepsilon \tag{2}$$

where $E_{\text{ox}}$ is the oxidation potential of the donor (aminostilbenes in this case) and $E_{\text{red}}$ is the reduction potential of the acceptor (Cu(II) in this case), $d$ is the center-to-center distance between donor and acceptor, and $\varepsilon$ is the dielectric constant of the solvent. In polar solvents, for example MeCN, the Coulombic term ($e^2/d\varepsilon$) can be neglected [38]. On the basis of the $E_{\text{red}}$ value of 0.96 V (vs SCE) for the Cu(II)/Cu(I) couple [39] and $E_{\text{ox}}$ values of 0.68, 0.64, and 0.66 V (vs SCE) for **1**–**3** (Fig. 3), respectively, the $\Delta G$ values for the Cu(II)-mediated oxidation of **1**–**3** are −0.28, −0.32, and −0.30 eV, respectively.

The nature of the chemical reactions associated with the radical cations of **1**–**3** in MeCN was also investigated. Various products were generated and the ESI-TOF mass spectra of $1 \times 10^{-3}$ M MeCN solutions of **2** ($m_2 = 315$) and **3** ($m_3 = 407$)

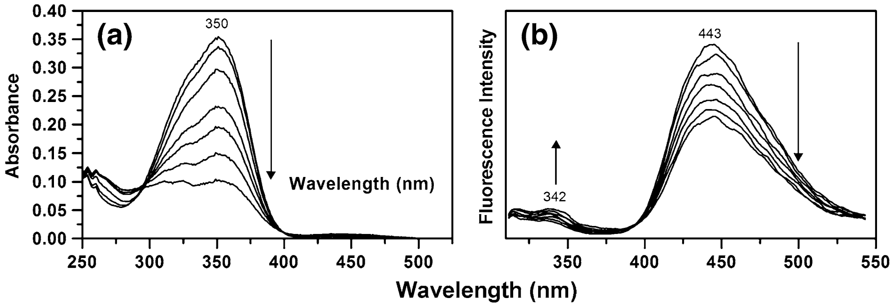
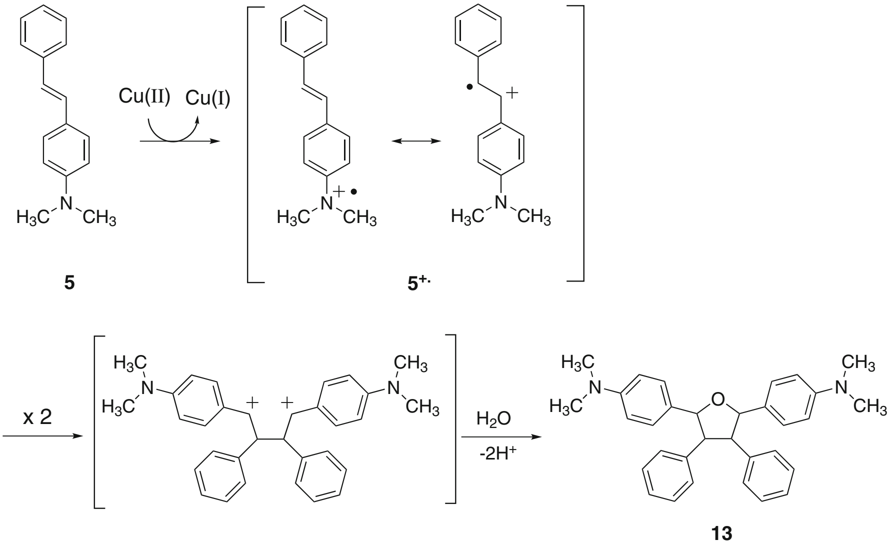


**Fig. 4** Absorption (**a**) and fluorescence (**b**) spectra of **5** ($1 \times 10^{-5}$ M, excitation at 295 nm) in MeCN on addition of 0, 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 equiv $Cu(ClO_4)_2 \cdot 6H_2O$

containing $2 \times 10^{-3}$ M Cu(II) suggests the presence of a dimeric form of **2** ($m/z = 647$) and **3** ($m/z = 831$). This is similar to the oxidative dimerization reactions of stilbene derivatives that form tetrasubstituted tetrahydrofuran species [40–42]. The oxidants could be metal oxides (e.g., $VOF_3$ and $FeCl_3 \cdot 6H_2O$) [40], stilbene oxidases or laccase [41], or nitrite ion [42]. The occurrence of the same reaction for **2** and **3** is, indeed, in agreement with the observed peaks in the mass spectra (i.e., $2m_{\mathbf{2}} + 16\ (O) + 1\ (H^+) = 647$ and $2m_{\mathbf{3}} + 16\ (O) + 1\ (H^+) = 831$). To isolate this product we used the structurally simpler compound, *N*,*N*-dimethylaminostilbene (**5**), because compound **5** ($m = 224$) has similar behavior to **2** in terms of Cu(II) titration absorption spectra (i.e., reduction of ICT band intensity and a noticeable increase in the baseline in the range 400–500 nm) (Fig. 4) and Cu(II)-mediated dimerization ($m/z = 463$). Compared with **2**, compound **5** is easier to synthesize and NMR analysis of its dimer product is more straightforward. The preparative oxidation reaction of **5** was performed at a concentration of $5 \times 10^{-5}$ M in the presence of 2.0 equiv $Cu(ClO_4)_2 \cdot 6H_2O$. The reactant was consumed after 12 h and the major product **13** (Scheme 2) was isolated by preparative HPLC with a yield of 72 %. Although there are four stereogenic centers in **13**, the NMR spectrum shows only one set of signals (Fig. 5a, b) and its regiochemistry can be determined on the basis of 2D NMR spectra (Fig. 5c, d). An attempt to grow single crystals of **13** was not successful, and thus the stereochemistry of the dimerization reaction could not be addressed. Scheme 2 shows our tentatively proposed mechanism for the Cu(II)-mediated dimerization reaction. The head-to-head dimerization with the anilino rather than phenyl groups located at the 2 and 5-positions of the tetrahydrofuran ring of **13** is consistent with the expectation of a more stable carbocation at the $\alpha$-position of the aminostilbenes. This is the first example of Cu(II)-mediated dimerization and tetrahydrofuran formation of aminostilbenes in MeCN.

The corresponding fluorescence responses of **1**–**3** to Cu(II) are also intriguing. As represented by **2** as example, addition of Cu(II) results in enhanced and blue-shifted fluorescence (Fig. 2b). The fluorescence intensity reaches a maximum by a factor of 20 ($\Phi_f = 0.1$) at ca 1.2 equiv Cu(II), and further addition of Cu(II) leads to fluorescence quenching. The fluorescence peak shifts from 577 to 408 nm at 1.2



**Scheme 2** Proposed mechanism for the Cu(II)-mediated dimerization reaction of compound **5**

equiv Cu(II). The large blue shift of fluorescence ($\Delta\lambda_f \approx 170$ nm) indicates that the new fluorescent species are of shorter conjugation length and/or weaker charge-transfer character than their precursors **1**–**3**. The new fluorescent species should have larger fluorescence quantum yield than **1** and **2** to account for the phenomenon of fluorescence enhancement. The observation of fluorescence quenching at higher concentrations of Cu(II) could be understood in terms of the fluorescence quenching nature of Cu(II) [11]. Because radical cations of arylamines are usually nonfluorescent in solutions at ambient temperature [43, 44] and the observed fluorescence is located at shorter wavelengths than the absorption of the radical cations, the new fluorescent species cannot be attributed to the radical cations of **1**–**3**. Consequently, a potential candidate is the tetrahydrofuran product. For example, $\lambda_f$ for *N*,*N*-dimethylaniline (DMA) in MeCN is 348 nm, which is close to the 355 nm fluorescence observed for **13** (Fig. 6). The somewhat longer fluorescence for **13** versus DMA could be attributed to the presence of a tetrahydrofuranyl group in the former. Likewise, the *N*-methyl-*N*-phenyl-*p*-anisidine group ($\lambda_f = 381$ nm, Fig. 6) in the dimerized product of **2** might be responsible for the 408 nm fluorescence induced by Cu(II) (Fig. 2b). Thus, the fluorescence peak maxima between 577 and 408 nm (e.g., 470 nm at 0.2 equiv Cu(II)) could be simply attributed to overlapping of fluorescence from intact **2** and the oxidized product. The immediate fluorescence response of **2** to Cu(II), even at a concentration as low as $10^{-5}$ M, indicates that formation of radical cation $\pi$-dimers is thermodynamically favorable, which drives the dimerization reactions proposed above. Similar absorption titration spectra were also observed for aminostilbenes **1** and **3** (Figs. 1a and 7a), although the corresponding fluorescence response is off–on and on–off (Figs. 1c and 7b), respectively. The different fluorescence response of **1**–**3** to Cu(II) reflects the different TICT character of their excited states (vide supra). No fluorescence

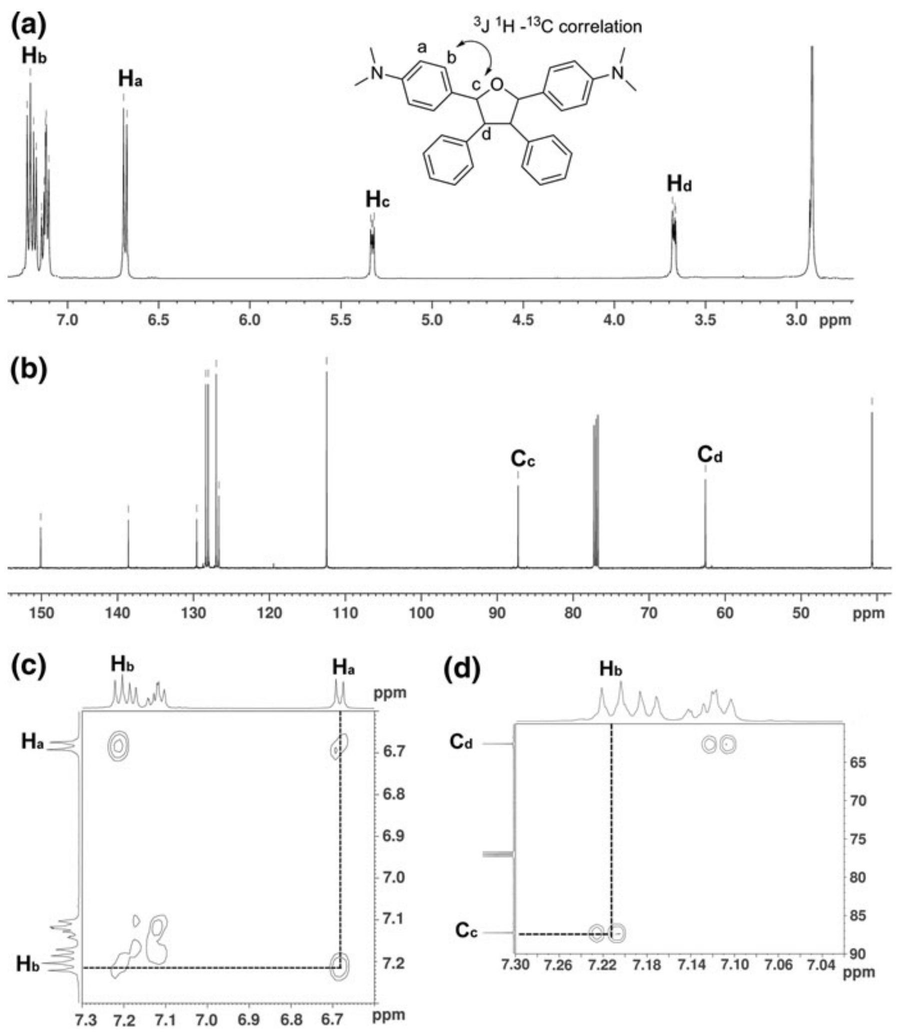


**Fig. 5** **a** $^1$H, **b** $^{13}$C, **c** COSY, and **d** HMBC NMR spectra of **13** in CDCl$_3$

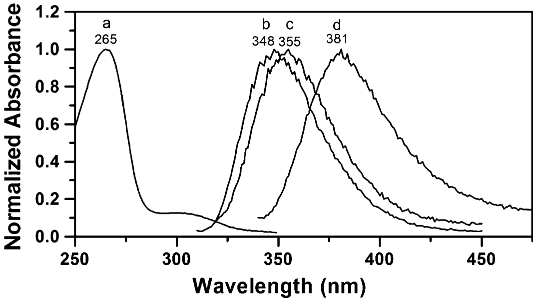


**Fig. 6** Normalized absorption spectra of **13** (**a**) and fluorescence spectra of **13** (**b**), *N*,*N*-dimethylaniline (**c**), and *N*-methyl-*N*-phenyl-*p*-anisidine (**d**) in MeCN

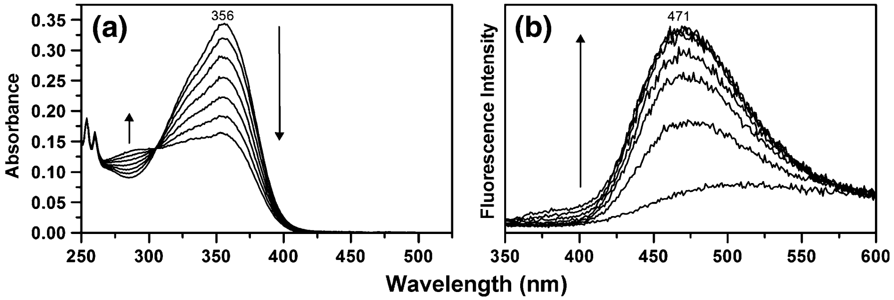


**Fig. 7** **a** Absorption and **b** fluorescence spectra of **1** ($1 \times 10^{-5}$ M, excitation at 303 nm) in MeCN on addition of 0, 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 equiv $Cu(ClO_4)_2 \cdot 6H_2O$

response is detectable for aminostilbenes **1**–**3** with other metal ions, including Mg(II), Ca(II), Ba(II), Ag(I), Co(II), and Ni(II).

With the above results in mind, it is interesting to investigate the fluorescence behavior of aminostilbenes containing a potential Cu(II) acceptor to address the relative importance of Cu(II)-mediated oxidation vs noncovalent Cu(II) binding. In this context, we targeted compound **4**, because the *o*-methoxybenzaldehyde acetylhydrazone moiety has been suggested to be a Cu(II)-selective acceptor [3, 10, 30]. Figure 8 shows the absorption and fluorescence titration spectra of **4** in MeCN with Cu(II). In conjunction with the observation of a mass peak at $m/z = 815$ for **4** ($m_4 = 399$), the great similarity in the responses of both absorption and fluorescence spectra to those of **2** suggests that the redox reaction discussed above for **1**–**3** is also responsible for the observed spectral changes in **4**. In other words, complexation of Cu(II) with **4**, if it occurs, does not inhibit oxidation of **4** by Cu(II). It should be noted that there is no change in the absorption spectra of **4** in the presence of 10 equiv Cu(II) in tris(hydroxymethyl)aminomethane)·HCl (10 mM, pH = 7.0) buffer containing 50 % (*v*/*v*) water–MeCN, which indicated that the redox reaction became negligible in aqueous solutions [19].

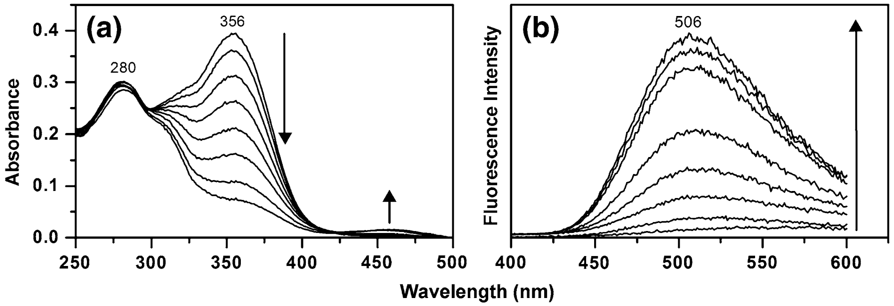


**Fig. 8** **a** Absorption and **b** fluorescence spectra of **4** ($1 \times 10^{-5}$ M, excitation at 303 nm) in MeCN on addition of 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.4 equiv $Cu(ClO_4)_2 \cdot 6H_2O$

## Conclusion

The spectroscopic behavior of a series of aminostilbenes (**1**–**5**) in response to Cu(II) has been reported. Cu(II)-mediated oxidation of **1**–**5** followed by dimerization and nucleophilic addition of water molecules account for changes in the electronic absorption and emission spectra, which is not affected by the presence of the potential Cu(II) receptor *o*-methoxybenzaldehyde acetylhydrazone. Thus, possible involvement of redox reactions should be taken into account in the signal-transduction mechanism of any Cu(II)-responsive and Cu(II)-oxidizable fluoroionophores in nonaqueous solutions. The dimerization reactions observed also provide a means of synthesis of substituted tetraarylfurans.

## Experimental

### General methods

Electronic spectra were recorded at room temperature (23 ± 1 °C). UV–visible spectra were measured on a Cary300 double beam spectrophotometer. Fluorescence spectra were recorded on a PTI QuantaMaster C-60 spectrometer and corrected for instrumental nonlinearity. The optical density (OD) of all solutions was approximately 0.1 at the wavelength of excitation. A $N_2$-outgassed solution of anthracene ($\Phi_f = 0.27$ in hexane) [45] was used as standard for determinations of fluorescence quantum yield and the solvent refractive index correction was applied. The excitation wavelength was 355 nm. An error of 10 % is estimated for the fluorescence quantum yields.

### Materials

All commercially available materials were used as received. Solvents for photochemical and electrochemical measurements were HPLC-grade. $CH_2Cl_2$ was dried over calcium hydride and distilled before use. The synthesis of aminostilbenes **1** and **2** has been reported [27]. Synthetic procedures and characterization data for new compounds are shown below.

#### *Compound* **3**

A mixture of **6** (0.52 g, 2.0 mmol), **7** (0.50 g, 2.2 mmol), NaO$^t$Bu (0.27 g, 2.8 mmol), DPPF (0.044 g, 0.040 mmol), and $Pd_2(dba)_3$ (0.018 g, 0.020 mmol) in 10 mL of anhydrous toluene under $N_2$(g) was heated at 90 °C for 12 h. The solution was cooled and the solvent was removed under reduced pressure to afford the crude product. Further purification was performed by column chromatography to provide the final product. Yellow solid; yield 95 %; mp 117–118 °C; $^1$H NMR (400 MHz, $CDCl_3$): 3.79 (s, 6H), 6.82 (dd, $J = 3.5$ and 12 Hz, 4H), 6.89–7.00 (m, 4H), 7.06 (d, $J = 9$ Hz, 4H), 7.20 (t, $J = 7.3$ Hz, 1H), 7.32 (t, $J = 7.3$ Hz, 4H), 7.46 (d, $J = 7.5$ Hz, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): 55.5, 114.7, 120.5, 126.1, 126.2, 126.6, 127.0, 127.2, 128.4, 128.6, 129.6, 137.9, 140.8, 148.3, 156.0 ppm; IR (KBr): 978, 1506, 1599 cm$^{-1}$; ESI-HRMS calcd for $C_{28}H_{25}NO_2$: 407.1885, found 407.1884.

*Compound **4***

A mixture of **12** (0.34 g, 1.0 mmol) and acethydrazide (0.15 g, 2.0 mmol) in absolute ethanol was stirred at RT for 12 h. Solvent was removed and the residue was purified by column chromatography ($CH_2Cl_2$–acetone = 20:1) to provide the final product. Pale yellow solid; yield 48 %; mp 210–212 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): 2.12/1.91 (s, 3H), 3.25 (s, 3H), 3.86 (s, 3H), 6.75 (m, 2H), 6.99 (d, $J = 16.0$ Hz, 1H), 7.11–7.22 (m, 4H), 7.33 (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 1H), 8.47/8.32 (s, 1H), 11.40/11.25 (s, 1H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): 20.7, 22.0, 56.4, 56.5, 113.7, 115.6, 115.9, 121.9, 123.7, 123.8, 125.1, 125.2, 126.4, 127.3, 127.6, 127.7, 127.88, 127.91, 128.4, 128.6, 128.8, 129.1, 138.1, 138.2, 141.2, 141.7, 141.9, 149.2, 155.0, 165.9, 172.3 ppm; IR (KBr): 959, 1590, 1671 cm$^{-1}$; ESI-HRMS calcd for $C_{25}H_{25}N_3O_2$: 399.1947, found 399.1943; Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16, H, 6.31, N, 10.52. Found: C, 75.02, H, 6.29, N, 10.51.

*Compound **11***

A mixture of **9** (0.98 g, 5.0 mmol), 5-bromoanisaldehyde (1.2 g, 5.5 mmol), $K_3PO_4$ (1.5 g, 7.0 mmol), **10** (0.025 g, 0.075 mmol), and $Pd_2(dba)_3$ (0.045 g, 0.050 mmol) in 20 mL anhydrous dioxane under $N_2$(g) was heated at 90 °C for 12 h. The solution was cooled and solvent was removed under reduced pressure to afford the crude product. Further purification was performed by column chromatography to provide the final product. Orange solid; yield 45 %; mp 190–192 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): 3.89 (s, 3H), 6.97–7.05 (m, 3H), 7.13–7.23 (m, 3H), 7.35 (t, $J = 7.6$ Hz, 2H), 7.42–7.48 (m, 4H), 7.54 (d, $J = 8.0$ Hz, 2H), 8.31 (s, 1H), 10.34 (s, 1H) ppm; 13C NMR (100 MHz, DMSO-$d_6$): 56.6, 114.5, 115.9, 116.5, 124.9, 125.3, 126.5, 127.3, 127.4, 128.2, 128.6, 128.9, 129.1, 136.7, 138.1, 144.2, 156.7, 198.4 ppm; IR (KBr): 3311, 2863, 1674, 1590, 967 cm$^{-1}$; ESI-HRMS calcd for $C_{22}H_{19}NO_2$: 329.1416, found 329.1412; Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22, H, 5.81, N, 4.25. Found: C, 80.02, H, 5.69, N, 4.21.

*Compound **12***

Sodium hydride (0.47 g, 12.0 mmol) was added slowly at 0 °C to a solution of **11** (0.99 g, 3.0 mmol) in 10 mL DMF and the mixture was stirred for 10 min. Iodomethane (0.60 mL, 9.0 mmol) was added, and stirring at RT was continued for 12 h. The reaction mixture was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Further purification was performed by column chromatography to provide the final product. Compound **12**: yield 70 %; mp 132–134 °C; $^1$H NMR (400 MHz $CDCl_3$): 3.94 (s, 3H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.93–6.98 (m, 2H), 7.06

(d, $J = 16.0$ Hz, 1H), 7.22 (t, $J = 7.3$ Hz, 1H), 7.32–7.40 (m, 5H), 7.49 (d, $J = 7.4$ Hz, 2H), 7.63 (s, 1H), 10.64 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): 40.4, 56.1, 113.0, 117.1, 123.0, 125.9, 126.2, 127.1, 127.5, 128.4, 128.6, 128.9, 131.9, 137.8, 142.1, 148.6, 158.3, 189.4 ppm; IR (KBr): 2859, 1685, 1593, 968 cm$^{-1}$; ESI-HRMS calcd for $C_{23}H_{21}NO_2$:343.1572, found 343.1572; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44, H, 6.16, N, 4.08. Found: C, 80.44, H, 5.99, N, 4.10.

### *Compound* ***13***

A solution of $Cu(ClO_4)_2{\cdot}6H_2O$ (0.0185 g, 0.05 mmol) in 5 mL MeCN was added dropwise to a solution of **5** (0.0558 g, 0.025 mmol) in 500 mL MeCN at RT, and mixture was stirred for 12 h. Solid $K_2CO_3$ (0.01 g, 0.075 mmol) was added, and the mixture was stirred for 0.5 h. MeCN was removed and the residue was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Further purification was performed by preparative HPLC (hexane–THF = 85:15) to provide the final product. Pale yellow solid; yield 72 %; mp 148–150 °C; $^1$H NMR (400 MHz, $CDCl_3$): 2.91 (s, 12H), 3.67 (dd, $J = 5.1$ and 2.2 Hz, 2H), 5.33 (dd, $J = 5.1$ and 2.2 Hz, 2H), 6.68 (d, $J = 7.0$ Hz, 4H), 7.10–7.14 (m, 6H), 7.18 (d, $J = 6.0$ Hz, 4H), 7.21 (d, $J = 7.0$ Hz, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): 40.6, 62.6, 87.3, 112.5, 126.6, 127.0, 128.0, 128.4, 129.6, 138.6, 150.1 ppm. ESI-HRMS calcd for $C_{32}H_{34}N_2O$:462.2671, found 462.2677.

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## References

1. M. Olivares, R. Uauy, Am. J. Clin. Nutr. **63**, 797S–811S (1996)
2. R. Uauy, M. Olivares, M. Gonzalez, Am. J. Clin. Nutr. **67**, 952S–959S (1998)
3. Y. Xiang, A. Tong, P. Jin, Y. Ju, Org. Lett. **8**, 2863–2866 (2006)
4. P. Li, X. Duan, Z. Chen, Y. Liu, T. Xie, L. Fang, X. Li, M. Yinb, B. Tang, Chem. Commun. **775**, 5–7757 (2011)
5. G. Hennrich, W. Walther, U. Resch-Genger, H. Sonnenschein, Inorg. Chem. **40**, 641–644 (2001)
6. Z. Xu, X. Qian, J. Cui, Org. Lett. **7**, 3029–3032 (2004)
7. R. Martínez, A. Espinosa, A. Tárraga, P. Molina, Tetrahedron **66**, 3662–3667 (2010)
8. I.-T. Ho, J.-H. Chu, W.-S. Chung, Eur. J. Org. Chem. **147**, 2–1481 (2011)
9. H. Zhang, L.-F. Han, K.A. Zachariasse, Y.-B. Jiang, Org. Lett. **7**, 4217–4220 (2005)
10. Z.-C. Wen, R. Yang, H. He, Y.-B. Jiang, Chem. Commun., 106–108 (2006)
11. A.W. Varnes, R.B. Dodson, E.L. Wehry, J. Am. Chem. Soc. **94**, 946–950 (1972)
12. Y. Xiang, A. Tong, Luminescence **23**, 28–31 (2008)
13. G. Ajayakumar, Ke. Sreenath, K.R. Gopidas, Dalton Trans., 1180–1186 (2009)
14. A.-F. Li, H. He, Y.-B. Ruan, Z.-C. Wen, J.-S. Zhao, Q.-J. Jiang, Y.-B. Jiang, Org. Biomol. Chem. **7**, 193–200 (2009)
15. E. Sanna, L. Martínez, C. Rotger, S. Blasco, J. González, E. García-España, A. Costa, Org. Lett. **12**, 3840–3843 (2010)
16. W. Lin, Li. Long, B. Chen, W. Tan, W. Gao, Chem. Commun. **46**, 1311–1313 (2010)
17. L.M. Hyman, C.J. Stephenson, M.G. Dickens, K.D. Shimizub, K.J. Franz, Dalton Trans. **39**, 568–576 (2010)
18. D. Wang, Y. Shiraishi, T. Hirai, Chem. Commun. **47**, 2673–2675 (2011)

19. S. Sumalekshmy, K.R. Gopidas, Chem. Phys. Lett. **413**, 294–299 (2005)
20. M. Kirchgessner, K. Sreenath, K.R. Gopidas, J. Org. Chem. **71**, 9849–9852 (2006)
21. K. Sreenath, C.V. Suneesh, V.K.R. Kumar, K.R. Gopidas, J. Org. Chem. **73**, 3245–3251 (2008)
22. K. Sreenath, C.V. Suneesh, K.R. Gopidas, R.A. Flowers II, J. Phys. Chem. A **113**, 6477–6483 (2009)
23. K. Sreenath, T.G. Thomas, K.R. Gopidas, Org. Lett. **13**, 1134–1137 (2011)
24. J.-S. Yang, Y.-D. Lin, Y.-H. Lin, F.-L. Liao, J. Org. Chem. **69**, 3517–3525 (2004)
25. J.-S. Yang, C.-Y. Hwang, M.-Y. Chen, Tetrahedron Lett. **48**, 3097–3102 (2007)
26. X. Liu, X. Shu, X. Zhou, X. Zhang, J. Zhu, J. Phys. Chem. A **114**, 13370–13375 (2010)
27. J.-S. Yang, K.-L. Liau, C.-M. Wang, C.-Y. Hwang, J. Am. Chem. Soc. **126**, 12325–12335 (2004)
28. J.-S. Yang, K.-L. Liau, C.-Y. Hwang, C.-M. Wang, J. Phys. Chem. A **110**, 8003–8010 (2006)
29. J.-S. Yang, K.-L. Liau, C.-Y. Li, M.-Y. Chen, J. Am. Chem. Soc. **129**, 13183–13192 (2007)
30. P.F. Lee, C.-T. Yang, D. Fan, J.J. Vittal, J.D. Ranford, Polyhedron **22**, 2781–2786 (2003)
31. F.D. Lewis, R.S. Kalgutkar, J.-S. Yang, J. Am. Chem. Soc. **121**, 12045–12053 (1999)
32. J.-S. Yang, S.-Y. Chiou, K.-L. Liau, J. Am. Chem. Soc. **124**, 2518–2527 (2002)
33. D.W. Old, M.C. Harris, S.L. Buchwald, Org. Lett. **10**, 1403–1406 (2000)
34. M.-K. Leung, C–.C. Chang, M.-H. Wu, K.-H. Chuang, J.-H. Lee, S.-J. Shieh, S.-C. Lin, C.-F. Chiu, Org. Lett. **8**, 2623–2626 (2006)
35. C.-C. Chang, H. Yueh, C.-T. Chen, Org. Lett. **13**, 2702–2705 (2011)
36. V. Balzani (ed.), *Electron Transfer in Chemistry*, vol. 1–5 (Wiley, New York, 2001)
37. M.A. Fox, M. Chanon (eds.), *Photoinduced Electron Transfer*, *Parts A–D* (Elsevier, Amsterdam, 1988)
38. G.J. Kavarnos, N.J. Turro, Chem. Rev. **86**, 401–449 (1986)
39. R.F. Nelson, R.H. Philp, J. Phys. Chem. **83**, 713–716 (1979)
40. S.S. Velu, I. Buniyamin, L.K. Ching, F. Feroz, I. Noorbatcha, L.C. Gee, K. Awang, I.A. Wahab, J.-F.F. Weber, Chem. Eur. J. **14**, 11376–11384 (2008)
41. R.t.H. Cichewicz, S.A. Kouzi, M.T. Hamann, J. Nat. Prod. **63**, 29–33 (2000)
42. L. Panzella, M.D. Lucia, C. Amalfitano, A. Pezzella, A. Evidente, A. Napolitano, M. d'Ischia, J. Org. Chem. **71**, 4246–4254 (2006)
43. H.J. Shire, D.-C. Zhao, J. Org. Chem. **55**, 4086–4089 (1990)
44. D.T. Breslin, M.A. Fox, J. Phys. Chem. **98**, 408–411 (1994)
45. W.R. Dawson, M.W. Windsor, J. Phys. Chem. **72**, 3251–3260 (1968)