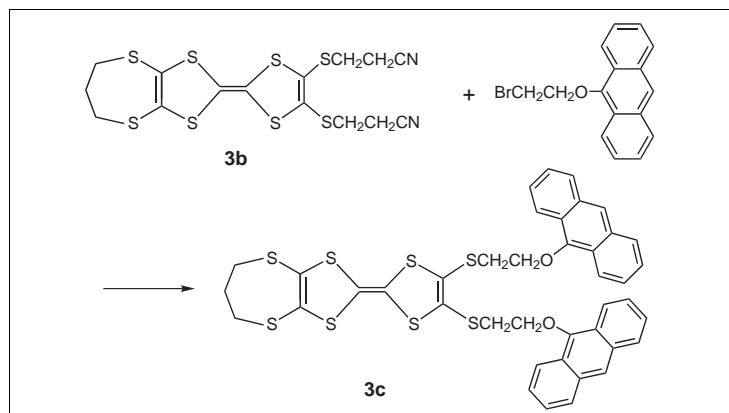


Wei Liu, Jing-Hua Lu, Ming Xu, Jing-Lin Zuo,* and Xiao-Zeng You*

Coordination Chemistry Institute and the State Key Laboratory of Coordination Chemistry, Nanjing University,
Nanjing 210093, China
E-mail: zuojl@nju.edu.cn
Received December 14, 2005



Three new fluorescence probes for $^1\text{O}_2$ with different electron-rich tetrathiafulvalene and anthracene units have been synthesized and characterized. Among them, compound **3c**, 2,3-bis[2-(9-anthryloxy)ethylthio]-6,7-(propylenedithio)-1,4,5,8-tetrathiafulvalene, is very sensitive and may act as the fluorescence probe for $^1\text{O}_2$.

J. Heterocyclic Chem., **43**, 1685 (2006).

Introduction.

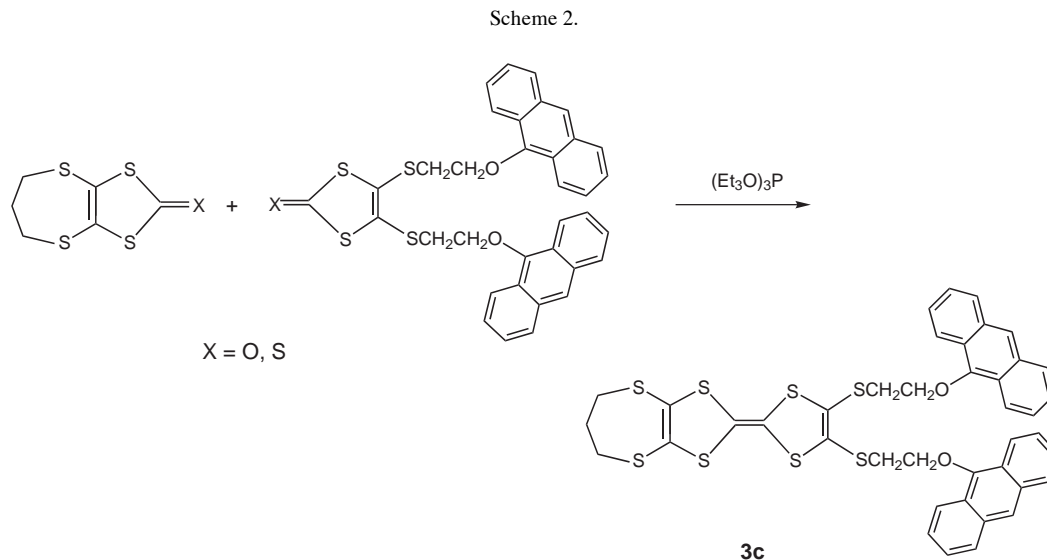
Singlet oxygen ($^1\text{O}_2$), an electronically excited form of molecular oxygen, has been well investigated for its unique reactivity and applications in organic synthesis [1]. Moreover, $^1\text{O}_2$ is also thought to be important in both biological and environmental processes as an active oxidant [2]. During the last decade, detection of $^1\text{O}_2$ has intrigued highly growing interest of more researchers [2,3]. Different types of molecular probes for $^1\text{O}_2$, mostly based on the changes of absorbance [4], fluorescence [1c,5], chemiluminescence [6], have been investigated. However, absorbance-based probes, such as 9,10-diphenylanthracene (DPA) [7], and furfuryl alcohol (FFA) [4b] are essentially less sensitive than luminescence detections. Comparatively, fluorescence probes are generally superior in terms of fast response, high sensitivity, ease of use and real-time detection [5,8].

Tetrathiafulvalenes (TTFs) are typical π -electron donors and have been extensively studied as organic conductors and superconductors [9]. They are also exploited as interesting and versatile components in host-guest chemistry, LB films, molecular switches, magnets, non-linear optics and LC materials [10]. Very recently, Zhu and his coworkers reported a highly selective and sensitive chemiluminescence trap for $^1\text{O}_2$ based on tetrathiafulvalene (TTF) substituted anthracene [3c], showing a 54-fold increase in fluorescence indicating $^1\text{O}_2$ trapping. The electron-rich TTF units will ease photoinduced electron transfer (PET) [8b] and thus be possible to facilitate the trap of $^1\text{O}_2$ by anthracene unit.

In order to find better $^1\text{O}_2$ traps, in this paper, we choose different extended tetrathiafulvalenedithiolene ligands with larger π -conjugation system to prepare a series of new anthracene derivatives (**1c**, **2c** and **3c**), expecting that they can exhibit preferable properties in trapping singlet oxygen ($^1\text{O}_2$). Indeed, the results of fluorescence measurements show that compound **3c**, 2,3-bis[2-(9-anthryloxy)ethylthio]-6,7-(propylenedithio)-1,4,5,8-tetrathiafulvalene, is highly sensitive to singlet oxygen, while the other two are not so sensitive, although strong fluorescence is also observed.

Results and Discussion.

As shown by schematic drawing (Scheme 1), the targeted three TTF-anthracene dyads were prepared. They are all unsymmetrical TTF derivatives. As we know, most reported TTF donors are symmetrical because of their ease of synthesis. During the past decades, there has been great effort on the preparation of varieties of functionalised unsymmetrical TTF. But they are still far less studied compared to the symmetric analogues, which is due to the difficulty and troublesome work in separation and purification of unsymmetrical TTF. In this paper, we adopted the cross-coupling method for the preparation of the protected bis(cyanoethylthio) TTFs. In consideration of less reactive thione, we optimized this reaction by coupling the 1,3-dithiole-2-thione and 1,3-dithiole-2-one to obtain TTF framework. The homo-coupling products have been observed and can be removed through column chromatography, since the polarity of the cyanoethyl

Possible synthetic approach for the preparation of **3c**

Electrochemistry.

The electrochemical characterization of compounds **1c**, **2c** and **3c** were measured by cyclic voltammetry. Figure 1 shows the cyclic voltammogram of compound **3c**, in which two reversible single-electron redox waves with $E_{1/2}^1 = 0.566 \text{ V}$, $E_{1/2}^2 = 0.834 \text{ V}$ and one irreversible oxidation peak ($E_{\text{ox}}^3 = 1.074 \text{ V}$) are observed. The first and second redox couples are due to the redox processes **3c**/**3c**⁺ and **3c**⁺/**3c**²⁺, respectively; while the irreversible oxidation potential can be ascribed to the oxidation of anthracene skeleton [11]. The cyclic voltammetry were also carried out for compound **1c** ($E_{1/2}^1 = 0.583 \text{ V}$, $E_{1/2}^2 = 0.866 \text{ V}$, $E_{\text{ox}}^3 = 1.164 \text{ V}$), and for **2c** ($E_{1/2}^1 = 0.553 \text{ V}$, $E_{1/2}^2$

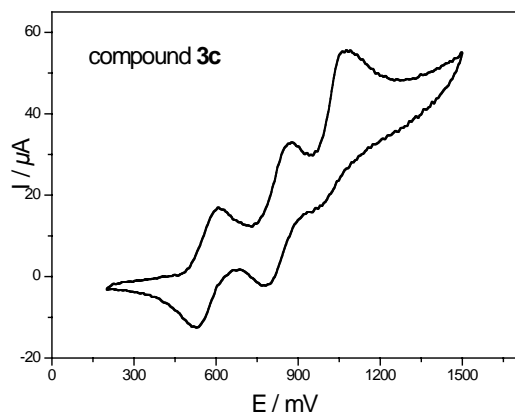


Figure 1. Cyclic voltammetry of **3c** with the concentration of $5 \times 10^{-4} \text{ M}$, measured in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1:1, v/v) solution, $n\text{-Bu}_4\text{NClO}_4$ (0.1 M) as the supporting electrolyte, platinum as the working and counter electrodes, Ag/AgCl as the reference electrode, at scanning rate 50 mV/s.

$= 0.813 \text{ V}$, $E_{\text{ox}}^3 = 1.140 \text{ V}$). As we know, the length and type of the side group on the TTF framework have considerable effect on their electrochemical properties. Compound **1c** shows the highest redox potential of these three compounds. It indicates that the increased numbers of S atoms in **2c** and **3c** enhance the delocalization of TTF core, and therefore making them (**2c**, **3c**) more easily to be oxidized than **1c**. Whereas, the benzene segment in **1c** has less effect on the increase of the π -electron density of TTF core.

UV-vis and Fluorescence.

Compared to compound 9-(2-bromoethoxy)-anthracene, the peaks at 350 nm, 370 nm and 390 nm in UV-vis spectra (Figure 2) for compounds **1c**, **2c** and **3c** are assigned to the absorption of anthracene skeleton. Moreover, the band around 320 nm for **1c**, 330 nm for **2c** and **3c** are due to the absorption of TTF moiety, respectively. It further confirms that the modification of TTF unit or that changes of the structural factors will result in the absorption band shift [12].

As shown in Figure 3, the maximum fluorescence excitation (λ_{ex}) of **3c** occurs at 400 nm and exhibits a weak emission at 435 nm, affording a low background signal due to the effective photoinduced electron transfer (PET) between TTF and anthracene units [11]. After reaction with $^1\text{O}_2$, a 10-fold increase in fluorescence was observed, resulting from the formation of endoperoxide that prohibits the PET process [3c,8b]. The distinct fluorescence increase clearly indicates that it can be used as a new probe for detecting $^1\text{O}_2$ efficiently, although it is less sensitive than the compound reported by Zhu *et al.* [3c].

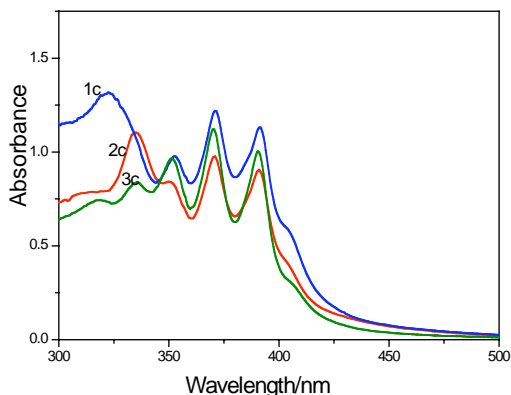


Figure 2. UV-vis Spectra of compounds **1c**, **2c**, **3c** and 9-(2-bromoethoxy)-anthracene; carried out in CH_2Cl_2 solution with a concentration of $1 \times 10^{-5} \text{ M}$.

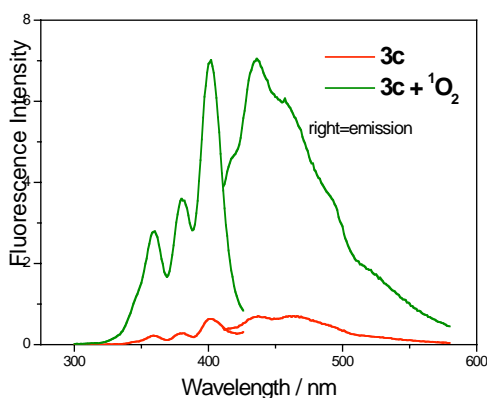


Figure 3. Fluorescence spectra of **3c** ($4 \times 10^{-6} \text{ M}$) before (red) and after (green) the reaction with $^1\text{O}_2$. (left=excitation, $\lambda_{\text{max}} = 400 \text{ nm}$; right=emission, $\lambda_{\text{max}} = 435 \text{ nm}$; performed at room temperature in 50 mM sodium phosphate buffer (PH = 7) containing 80% THF as a cosolvent; $^1\text{O}_2$ was chemically generated from the $\text{H}_2\text{O}_2/\text{NaOCl}$ (1 mM/10 mM) system in neutral and alkaline media [13].

But there is no significant fluorescence increase for compounds **1c** and **2c** after the addition of $^1\text{O}_2$. Only 2-fold fluorescence enhancement is observed for **1c**. For **2c**, the fluorescence intensity even decreases slightly after the reaction with $^1\text{O}_2$. The three compounds reported here have similar structures, but show very different fluorescence properties after the reaction with $^1\text{O}_2$. Therefore, it is possible for us to optimize and explore better probes by the slight modifications on TTF derivatives.

EXPERIMENTAL

General Procedure.

Melting points were determined with a X-4 digital micro melting point apparatus. Elemental Analyses for C, H were

performed on a Perkin-Elmer 240C analyzer. The IR spectra were taken on a Vector22 Bruker Spectrophotometer ($400\text{--}4000\text{cm}^{-1}$) with KBr pellets. MALDI-TOF-MS spectra were determined with Voyager-DETM STR instrument. Absorption spectra were measured with a UV-3100 spectrophotometer. Fluorescence measurements were carried out on AMINCO Bowman Series 2 Luminescence Spectrometer in a 1-cm quartz cell. NMR spectra were measured on a Bruker AM 500 spectrometer. Cyclic voltammetry data were recorded by an EG&G PAR Model 273 electrochemical analytical instrument.

Reagent-grade tetrahydrofuran and methanol were purified and distilled with standard methods. $\text{P}(\text{EtO})_3$ was freshly distilled before use. Other solvents and chemicals were purchased from commercial sources and used as received.

1a, **1b**, **2a**, **2b**, **3a**, **3b**, 4,5-Bis(2-cyanoethylthio)-1,3-dithiole-2-one and 9-(2-bromoethoxy)-anthracene were synthesized according to the literature [14-16]. Schlenk techniques were used in carrying out manipulation under inert atmosphere.

2,3-Bis[2-(9-anthryloxy)ethylthio]-6,7-benzotetrathiafulvalene (**1c**).

Under nitrogen atmosphere, to a solution of **1b** (0.297 g, 0.7 mmol) in THF (60 mL) was added a solution of $\text{CsOH} \cdot \text{H}_2\text{O}$ (0.258, 1.54 mmol) in methanol (5 mL) over a period of 1 h. The mixture was stirred for an additional 1 h and during which a solution of 9-(2-bromoethoxy)-anthracene (0.527 g, 1.75 mmol) in 10 mL of THF was added. The reaction mixture was further stirred overnight at room temperature. The resulting light yellow precipitate was filtered off and the residue solution was concentrated. After the addition of 10 mL of MeOH, yellow precipitate was obtained. Purification by column chromatography (CH_2Cl_2 /ethyl acetate) on silica gel gave **1c** as yellow solid (0.16 g, 30% based on compound **1b**). Mp: $83\text{--}86^\circ\text{C}$; IR (KBr, cm^{-1}): 1621(C=C), 1557, 1443, 1411(C-S), 1338, 1277, 1164, 1090, 1001, 879, 773, 737, 674, 551; ^1H NMR (500 MHz, CDCl_3 , ppm): δ 3.50(m, 4H), 4.42(m, 4H), 7.16(m, 4H), 7.45(m, 8H), 7.96(d, 4H), 8.21(s, 2H), 8.36(m, 4H); ^{13}C NMR (500 MHz, CDCl_3 , ppm): δ 36.61, 74.24, 122.33, 122.65, 123.00, 123.32, 124.95, 125.40, 125.89, 126.41, 128.81, 132.70, 136.87, 150.64; Calcd. for $\text{C}_{42}\text{H}_{30}\text{O}_2\text{S}_6$: 759.08; MALDI-TOF: 758.0; Found: C, 66.32; H, 3.96; Calcd.: C, 66.46; H, 3.98.

2,3-Bis[2-(9-anthryloxy)ethylthio]-6,7-(ethylenedithio)-1,4,5,8-tetrathiafulvalene (**2c**).

Compound **2c** was prepared using the same conditions as described above for compound **1c**, but **2b** was used instead of **1b**. It was isolated as orange yellow solid in 40% yield (0.283 g). Mp: $63\text{--}67^\circ\text{C}$; IR (KBr, cm^{-1}): 1620(C=C), 1555, 1460, 1440, 1410(C-S), 1337, 1271, 1162, 109, 879, 770, 736, 549; ^1H NMR (500 MHz, CDCl_3 , ppm): δ 3.42 (m, 4H), 3.89 (t, 4H); 4.55(t, 4H), 7.51(m, 8H), 8.02(d, 4H); 8.28 (s, 2H); 8.36 (m, 4H). ^{13}C NMR (500 MHz, CDCl_3 , ppm): δ 29.71, 30.23, 30.34, 74.73, 121.85, 122.24, 122.53, 124.16, 124.23, 124.66, 125.14, 127.25, 128.04, 129.30, 130.04, 131.91, 149.83; Calcd. for $\text{C}_{40}\text{H}_{30}\text{O}_2\text{S}_8$: 799.19; MALDI-TOF: 798.82; Found: C, 59.94; H, 3.77; Calcd.: C, 60.11; H, 3.78.

2,3-Bis[2-(9-anthryloxy)ethylthio]-6,7-(propylenedithio)-1,4,5,8-tetrathiafulvalene (**3c**).

The procedure of preparation of compound **3c** is similar to that of compounds **1c** and **2c**. Pure compound **3c** was obtained in 26%

yield (0.106 g). Mp. 87–89°C; IR (KBr, cm^{-1}): 1621(C=C), 1557, 1439, 1412(C–S), 1338, 1276, 1167, 1091, 1000, 880, 772, 736, 550; ^1H NMR (500 MHz, CDCl_3 , ppm): δ 2.42(s, 2H), 2.71(d, 4H), 3.42(t, 4H), 4.37(t, 4H), 7.44(m, 8H), 7.97(m, 4H), 8.20(s, 2H), 8.29(m, 4H); ^{13}C NMR (500 MHz, CDCl_3 , ppm): δ 29.36, 32.73, 34.01, 35.79, 73.44, 121.85, 122.24, 122.52, 124.16, 124.23, 124.66, 125.14, 127.25, 128.04, 129.30, 130.04, 131.91, 149.83; Calcd. for $\text{C}_{41}\text{H}_{32}\text{O}_2\text{S}_8$: 813.2; MALDI-TOF: 812.3; Found: C, 60.48; H, 3.96; Calcd.: C, 60.55; H, 3.97.

Acknowledgements.

This work was supported by The Major State Basic Research Development Program (G2006CB806104) and the National Natural Science Foundation of China. J. -L. Zuo thanks the Program for New Century Excellent Talents in University of China.

REFERENCES AND NOTES

- [1a] M. Prein, W. Adam, *Angew. Chem. Int. Ed.*, **35**, 477–494 (1996); [b] A. A. Frimer, *Singlet Oxygen*; CRC Press: Boca Raton, FL, (1997); [c] N. Umezawa, K. Tanaka, Y. Urano, K. Kikuchi, T. Higuchi, T. Nagano, *Angew. Chem. Int. Ed.*, **38**, 2899–2901 (1999); [d] C. Schweitzer, R. Schmidt, *Chem. Rev.*, **103**, 1685–1757 (2003) and references therein.
- [2a] N. V. Blough, R. G. Zepp, In *Active Oxygen: Reactive Oxygen Species in Chemistry*; C. S. Foote, J. S. Valentine, A. Greenberg, S. F. Liebman, Eds.; Blackie Academic and Professional: London, (1995); [b] P. Kang, C. S. Foote, *J. Am. Chem. Soc.*, **124**, 4865–4873, (2002); [c] P. Wentworth, J. E. McDunn, A. D. Wentworth, C. Takeuchi, J. Nieva, T. Jones, C. Bautista, J. M. Ruedi, A. Gutierrez, K. D. Janda, B. M. Babior, A. Eschenmoser, R. A. Lerner, *Science*, **298**, 2195–2199 (2002); [d] D. A. Pratt, J. H. Mills, N. A. Porter, *J. Am. Chem. Soc.*, **125**, 5801–5810 (2003); [e] L. A. MacManus-Spencer, D. E. Latch, K. M. Kroncke, K. McNeill, *Anal. Chem.* **77**, 1200–1205. (2005).
- [3] See for examples: [a] V. Nardello, N. Azaroual, I. Cervoise, G. Vermeersch, J. M. Aubry, *Tetrahedron*, **52**, 2031–2046 (1996); [b] J. P. Roth, R. Wincek, G. Nodet, D. E. Edmondson, W. S. McIntire, J. P. Klinman, *J. Am. Chem. Soc.*, **126**, 15120–15131 (2004); [c] X. Li, G. Zhang, H. Ma, D. Zhang, J. Li, D. Zhu, *J. Am. Chem. Soc.*, **126**, 11543–11548 (2004).
- [4] See for examples: [a] R. G. Zepp, N. L. Wolfe, G. L. Baughman, R. C. Hollis, *Nature*, **267**, 421–423 (1977); [b] W. R. Haag, J. Hoigne, *Environ. Sci. Technol.*, **20**, 341–348. (1986); [c] K. Denham, R. E. Milofsky, *Anal. Chem.*, **70**, 4081–4085. (1998).
- [5] K. Tanaka, T. Miura, N. Umezawa, Y. Urano, K. Kikuchi, T. Higuchi, T. Nagano, *J. Am. Chem. Soc.*, **123**, 2530–2536 (2001).
- [6] See for examples: [a] T. Goto, T. Takagi, *Bull. Chem. Soc. Jpn.*, **53**, 833–834 (1980); [b] W. Adam, I. Bronstein, B. Edwards, T. Engel, D. Reinhardt, F. W. Schneider, A. V. Trofimov, R. F. Vasil'ev, *J. Am. Chem. Soc.*, **118**, 10400–10407 (1996); [c] N. Watanabe, H. Suganuma, H. Kobayashi, H. Mutoh, Y. Katao, M. Matsumoto, *Tetrahedron*, **55**, 4287–4298 (1999); [d] S. Miyamoto, G. R. Martinez, A. P. B. Martins, M. H. G. Medeiros, P. Di Mascio, *J. Am. Chem. Soc.*, **125**, 4510–4517 (2003).
- [7] M. J. Steinbeck, A. U. Khan, M. J. Karnovsky, *J. Biol. Chem.*, **267**, 13425–13433 (1992).
- [8] See for examples: [a] R. Y. Tsien, In *Fluorescent and Photochemical Probes of Dynamic Biochemical Signals Inside Living Cells*; A. W. Czarnik, Ed.; American Chemical Society: Washington, DC, 1993; pp 130–146; [b] A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.*, **97**, 1515–1566 (1997); [c] S. Uchiyama, G. D. McClean, K. Iwai, A. P. de Silva, *J. Am. Chem. Soc.*, **127**, 8920–8921 (2005); [d] E. Sasaki, H. Kojima, H. Nishimatsu, Y. Urano, K. Kikuchi, Y. Hirata, T. Nagano, *J. Am. Chem. Soc.*, **127**, 3684–3685 (2005).
- [9] See for reviews: [a] X. Z. You, Y. Zhang, In *Advances in Transition Metal Coordination Chemistry*; C. M. Che, Ed.; JAI Press Inc.: Greenwich, CT, 1996; pp 239–286; [b] T. Mori, *Chem. Rev.*, **104**, 4947–4970 (2004); [c] J. -i. Yamada, H. Akutsu, H. Nishikawa, K. Kikuchi, *Chem. Rev.*, **104**, 5057–5083 (2004); [d] A. Kobayashi, E. Fujiwara, H. Kobayashi, *Chem. Rev.*, **104**, 5243–5264 (2004); [e] R. P. Shibaeva, E. B. Yagubskii, *Chem. Rev.*, **104**, 5347–5378 (2004); [f] E. Coronado, P. Day, *Chem. Rev.*, **104**, 5419–5448 (2004).
- [10a] J. L. Segura, N. Martín, *Angew. Chem., Int. Ed.*, **40**, 1372–1409 (2001); [b] J. -i. Yamada, T. Sugimoto, *TTF Chemistry: Fundamentals and Applications of Tetrathiafulvalene* Kodansha Ltd: Tokyo and Springer-Verlag: Berlin, Heidelberg, New York 2004; [c] E. Coronado, F. Palacio, J. Veciana, *Angew. Chem. Int. Ed.*, **42**, 2570–2572 (2003); [d] M. Bendikov, F. Wudl, D. F. Perepichka, *Chem. Rev.*, **104**, 4891–4945 (2004); [e] J. O. Jeppesen, M. B. Nielsen, J. Becher, *Chem. Rev.*, **104**, 5115–5131 (2004); [f] D. R. Talham, *Chem. Rev.*, **104**, 5479–5501 (2004).
- [11] G. Zhang, D. Zhang, X. Guo, D. Zhu, *Org. Lett.*, **6**, 1209–1212 (2004).
- [12] J. -L. Zuo, T. -M. Yao, F. You, X. -Z. You, H. K. Fun, B. C. Yip, *J. Mater. Chem.*, **6**, 1633–1637 (1996).
- [13] A. M. Held, D. J. Halko, J. K. Hurst, *J. Am. Chem. Soc.*, **100**, 5732–5740 (1978).
- [14] J. Nakayama, H. Sugiura, M. Hoshino, *Tetrahedron Lett.*, **24**, 2585–2588 (1983).
- [15a] M. Kumasaki, H. Tanaka, A. Kobayashi, *J. Mater. Chem.*, **8**, 301–307 (1998); [b] H. -R. Wen, J. -L. Zuo, T. -A. Scott, H. -C. Zhou, X. -Z. You, *Polyhedron*, **24**, 671–677 (2005).
- [16] W. H. Pirkle, J. M. Finn, *J. Org. Chem.*, **48**, 2779–2780 (1983).