Configuration Determination

DOI: 10.1002/anie.201408398

Axially Chiral BODIPY DYEmers: An Apparent Exception to the Exciton Chirality Rule**

Torsten Bruhn, Gennaro Pescitelli,* Sandro Jurinovich, Anu Schaumlöffel, Franziska Witterauf, Johannes Ahrens, Martin Bröring, and Gerhard Bringmann**

Abstract: *The exciton chirality method (ECM) is commonly recognized as one of the best approaches to assign the absolute configuration of biaryls. This paper reports the first exception to this method for a simple biaryl system. ECD and VCD measurements in combination with DFT (B3LYP/6-311G*), TDDFT (CAM-B3LYP/6-311G*), and Coupled-Cluster (RI-SCS-CC2) calculations were used to determine the absolute configurations of axially chiral BODIPY DYEmers. The ECM fails to predict the sign of the intense CD couplet at 500 nm of the 1,1′-coupled dimer. The odd behavior was rationalized by considering the strong transition magnetic dipole associated with the 500 nm transition, which leads to an unexpected dominance of the μm coupling at the expense of the μμ one in these compounds. This is the first case in which a strong μm coupling hampers the use of the ECM, but this behavior should not be restricted to the BODIPY chromophore.*

The boron dipyrrin complex (BODIPY, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) was first described by Treibs and Kreuzer in 1968.[1] Since the late 1990s this fluorescent dye has become a topic of growing research, due to its unique properties and its high potential in manifold applications.[2] Several recent publications have dealt with quantum-chemical investigations of BODIPYs using TDDFT methods with a focus on the absorption and fluorescence properties of monomeric species.[3] In nearly all cases circular dichroism (CD) has been used to merely prove the existence of chirality. Hitherto known examples of chiral BODIPYs include monomers with central, axial, and helical chirality[4] and multichromophoric systems bound to chiral building blocks.[5] Also, axial chirality has been introduced to BODIPY dimers and polymers via chiral binaphthyls.[6] In contrast, the C–C-coupled dimers reported herein possess an intrinsic axial chirality. In no case so far has the absolute configuration (AC) of chiral dimeric BODIPYs been assigned by the comparison of calculated CD curves with experimental ones and the use of the exciton chirality method[7] was mentioned only in one case.[8]

The BODIPY DYEmers[9] (Figure 1) were synthesized according to the literature[10] by oxidative C–C coupling of the corresponding monomers at the nonsubstituted pyrrolic positions. The groups next to the axis prevent free rotation about this bond in the dimers, leading to racemic mixtures of configurationally stable atropisomers.

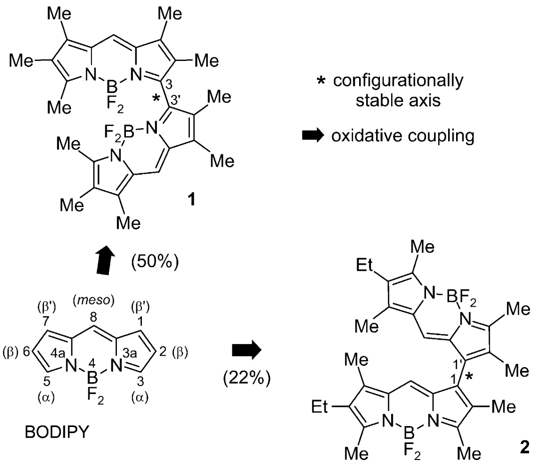

Figure 1. Axially chiral BODIPY DYEmers and their formation from the appropriate monomeric building block.

The dimeric compounds **1** and **2** were initially resolved by HPLC on a chiral phase followed by electronic circular dichroism (ECD) measurements in the stopped-flow mode. Significant differences were found in the CD spectra for the two dimers. While the α-dimer **1** (3,3′-coupled) showed an intense ECD couplet (i.e., two bands of opposite sign) at around 510 nm, the intensities of the ECD bands of the β′-dimer **2** (1,1′-coupled) were quite small. Offline ECD measurements confirmed that the normalized (Δε units) CD spectrum of **2** is smaller than that of **1** by a factor of 5 (see the Supporting Information), which was unexpected as both compounds feature a rather similar orientation of the very same chromophores.

The intense ECD couplet of the α-dimer can be explained by a strong coupling of the transition dipole moments of the chromophores. The ECD couplet amplitude (peak-to-trough

---

[*] Dr. T. Bruhn, A. Schaumlöffel, F. Witterauf, Prof. Dr. G. Bringmann
Institut für Organische Chemie, Universität Würzburg
Am Hubland, 97074 Würzburg (Germany)
E-mail: torsten.bruhn@uni-wuerzburg.de
bringman@chemie.uni-wuerzburg.de
Dr. G. Pescitelli, S. Jurinovich
Dipartimento di Chimica e Chimica Industriale
Università di Pisa, via Moruzzi 3, 56124 Pisa (Italy)
E-mail: gennaro.pescitelli@unipi.it
Dr. J. Ahrens, Prof. Dr. M. Bröring
Institut für Anorganische und Analytische Chemie
Technische Universität Braunschweig
Hagenring 30, 38106 Braunschweig (Germany)

[**] This work was supported by the DFG. We thank Prof. Dr. Lorenzo Di Bari, Prof. Dr. Benedetta Mennucci and Dr. Ciro A. Guido for fruitful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408398.

difference in $\Delta\varepsilon$ units) amounts to $575\,\mathrm{M}^{-1}\mathrm{cm}^{-1}$, a remarkably high value even for a biaryl.[11] The strong couplet suggested the use of the exciton chirality method (ECM)[7] for determining the AC of the 3,3′-coupled BODIPY dimer **1**. The main transition of the BODIPY monomer is polarized along the long axis, as determined by TDDFT calculations on the monomer. Thus, the dimer *M*-**1** should show a negative couplet in the ECD spectrum and *P*-**1** a positive one. The faster eluting compound clearly exhibits a negative couplet (Figure 2), and is thus *M*-configured, while the slower enantiomer displays a mirror-image CD curve (see the Supporting Information) and has the *P*-configuration.

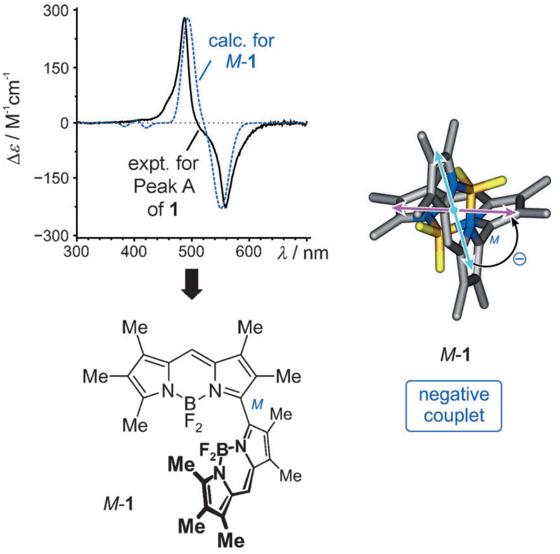

Figure 2. Determination of the AC of the faster resolving enantiomer of dimer **1** by the ECM and by comparison of the calculated CD spectrum (TDCAM-B3LYP/6-311+G*) with the experimental spectrum.

In addition, quantum-chemical CD calculations were performed. The conformational analysis of the *M*-configured enantiomer of **1** using B3LYP/6-311+G* gave only one relevant conformer, with an axial dihedral angle N3a-C3-C3′-N3a′ of 103°. Subsequent TDCAM-B3LYP/6-311+G*[CPCM,CH_2Cl_2] calculations of the conformer yielded a CD spectrum that closely matched (Δ_{ESI}[12] $= 86\,\%$) the experimental CD curve of the faster eluting enantiomer, fully corroborating the results of the ECM.

Similar application of the ECM to the β'-dimer **2** would predict *M*-chirality for the second eluted enantiomer, showing a negative exciton couplet around 530 nm (Figure 3 and Figure 4). The reversal of the elution order with respect to **1**, and the already mentioned strong intensity difference in the ECD spectra of the two dimers, called, however, for special caution in dealing with compound **2**. A conformational analysis of the *M*-configured enantiomer found two conformations differing in their dihedral angle. The main conformer (**2a**) with about 98 % population at 300 K (according to Gibbs free energies) has an angle of −116° (C8a-C1-C1′-C8a′) while the less populated conformer (**2b**) has an angle of −58°. According to the ECM, a negative couplet was expected for

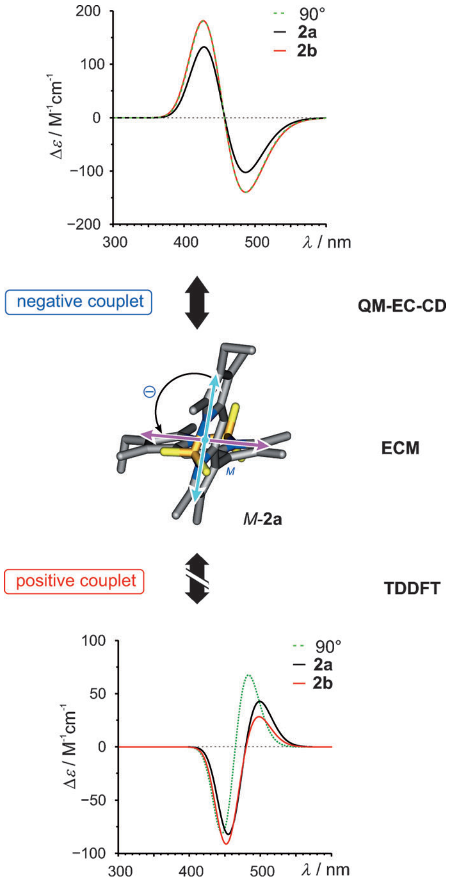

Figure 3. Comparison of the results of the ECM with those of QM-EC-CD and TDCAM-B3LYP calculations for dimer **2**. TDDFT contradicts both ECM and QM-EC-CD findings.

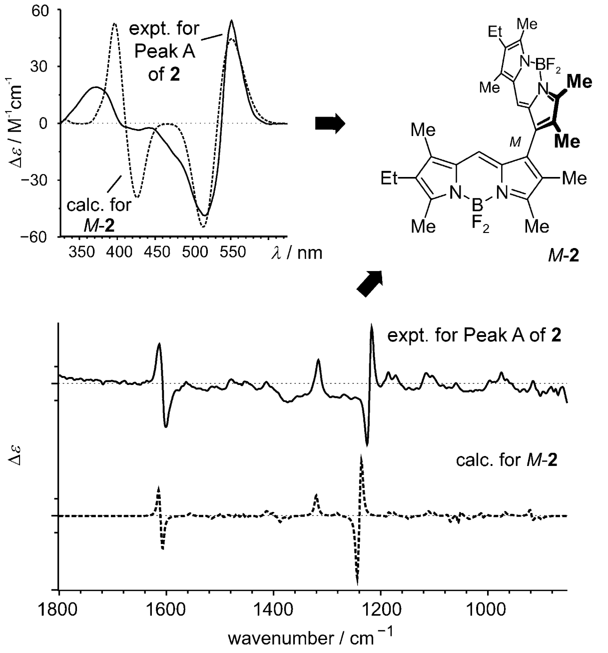

Figure 4. Comparison of experimental ECD and VCD spectra with the calculated spectra (RI-SCS-CC2/def2-SVP for ECD, B3LYP/6-311G* for VCD) of compound *M*-**2**.

both conformations (shown in Figure 3 for the major conformer) and, therefore, it was all the more surprising that the TDCAM-B3LYP calculations yielded positive couplets of similar intensity for both conformers (Figure 3). To exclude the possible role of conjugation between the chromophoric halves, a third conformer with a restrained dihedral angle of 90° (for which conjugation is not possible) was used for a TDDFT calculation, which again led to a positive calculated ECD couplet (Figure 3).

To exclude potential problems from the DFT method and the use of the "visual" ECM, two different approaches were considered. First, RI-SCS-CC2/def2-SVP calculations were performed (Figure 4). These were in agreement with the TDDFT findings. Secondly, quantitative QM-EC-CD (exciton-coupled circular dichroism) computations were carried out using a fragmentation procedure where the excitonic Hamiltonian, built using TDCAM-B3LYP-computed transition densities and energies, is explicitly solved.[13] The method includes solvation effects and static substituent perturbation (see the Supporting Information for details). QM-EC-CD computations fully confirmed the expectations from the ECM (Figure 3), and further contradicted TDDFT and SCS-CC2 calculations. Although we were reasonably confident that at least SCS-CC2 calculations were accurate enough to predict the AC of the β′-dimer **2**, an independent confirmation by vibrational circular dichroism (VCD) spectroscopy was necessary.[14]

VCD spectra were recorded in CCl_4 solution and compared with the spectra from B3LYP/6-311+G* calculations (averaged over two conformers, Figure 4 and the Supporting Information). The computed VCD curve of the *M*-enantiomer fits the experimental spectrum of the faster eluting compound (Peak A) very well. This is the same AC predicted by TDDFT and CC2 calculations (Figure 4 and the Supporting Information). Thus, VCD confirmed the full ECD computations and clearly proved that the ECM fails for this BODIPY dimer.

To understand this failure, one has to take a closer look at the theoretical background of the exciton chirality method. The rotational strengths $\mathbf{R}^{\alpha}$ and $\mathbf{R}^{\beta}$ of the two excited states of an exciton couplet are defined by Equation (1).[7]

$$\begin{aligned}\mathbf{R}^{\alpha,\beta} =& \pm\frac{1}{2}\,\pi\,\sigma_0\,\mathbf{R}_{ij}\cdot(\boldsymbol{\mu}_{ioa}\times\boldsymbol{\mu}_{joa})\\ &+\frac{1}{2}\,Im\,\{(\boldsymbol{\mu}_{ioa}\mp\boldsymbol{\mu}_{joa})\cdot(\mathbf{m}_{ioa}\mp\mathbf{m}_{joa})\}\end{aligned} \tag{1}$$

Here, $\boldsymbol{\mu}$ and $\mathbf{m}$ are the electric and magnetic transition dipole moments, respectively, of the chromophores *i* and *j*, and $\mathbf{R}_{ij}$ is the interchromophoric distance vector.[7] The first term of the equation (μμ term) describes the rotational strength obtained by combining the electric transition moments of the individual chromophores with the origin-dependent magnetic moments generated thereby. The second term (μm term) describes the rotational strength obtained from the scalar product of the excitonic electric and origin-independent magnetic transition moments, which result from the in-phase and anti-phase combinations of the individual chromophores.

In the standard application of the ECM, one assumes that the intrinsic (origin-independent) magnetic transition moment $m_{0\alpha}$ for the $0\rightarrow\alpha$ excitation is negligible. This is certainly the case for most aromatic π–π* excitations to which the ECM has been applied, such as the most intense long-axis-polarized transition in *p*-substituted benzoates, naphthoates, anthroates, and so on. Thus, the μm term is ignored and only the μμ coupling determines the rotational strengths of an exciton couplet, and, after multiplication with the coupling potential V_{ij}, the sign and intensity of the couplet.[7] However, the BODIPY S_0–S_1 transition at 500 nm is associated with a strong magnetic transition dipole moment perpendicular to the aromatic plane. The calculated magnetic moment amounts to 1.85 au from TD CAM-B3LYP and to 2.23 au from RI-SCS-CC2 (for comparison, the CAM-B3LYP-calculated value of the magnetic-dipole allowed n–π* transition of acetone or formaldehyde is 1.21 au). In this situation, it is clear that the rotational strengths R^{α} and R^{β} have to be calculated by using the full equation, including both μμ and μm couplings.

Since this is hardly done by visual inspection of the molecule, the software used in the above-mentioned fragmentation procedure was modified to take intrinsic magnetic moments into account (see the Supporting Information).[15] In this way, the overall coupling, which includes both μμ and μm terms, is evaluated (Table 1). Most interestingly, the μm term was found to be larger than the μμ term. In the case of the 3,3′-coupled **1**, the values are of same sign and their sum generates large total rotational strengths, which explain the high ECD amplitudes found in the experiment and in the full calculations. By contrast, the two terms have opposite signs for the 1,1′-coupled dimer **2**, and thus, the μm coupling dominates over the μμ term. In this situation, the overall couplet has a sign opposite to that predicted by the ECM, and its intensity is strongly reduced (in comparison with the 3,3′-coupled dimer **1**), as found experimentally.

Table 1: Rotational strength values (10^{-40} esu^{2}cm^{-2}) of the QM-EC-CD calculated first excited states of the *M*-configured enantiomers of **1** and **2** using the TDDFT/fragmentation method.[15]

	E [eV]	μμ	Total
1	2.59	−862.3	−1960.6
	2.95	983.3	1695.0
2a	2.67	−878.2	302.4
	2.79	919.2	−227.4
2b	2.65	−857.9	250.5
	2.82	912.4	−216.4

Although a few "exceptions" or failures have been claimed to be observed for the ECM in the literature,[16,17] most of them concern cases plagued by conformational ambiguity[16] or by the presence of several overlapping transitions.[17] This is the very first case where the exciton chirality method fails for a simple biaryl compound with an established conformation and for a transition well separated from others. As shown above, this is not because of an intrinsic failure of the method, but because of the occurrence of a different source of optical activity. The importance of the μm term for dimer **2** is based on a unique combination of a strong magnetic transition dipole moment with a short interchromophoric distance (the ECD associated with the μm term scales with the potential V_{ij} and thus with R_{ij}^{-3}).[7] To show the importance of this latter aspect, we performed TDCAM-B3LYP/6-31G* calculations on a model of M-**2** in which the 1,1′ bond was cut, the C1–C1′ distance elongated to 4 Å, and the resulting separated chromophores each saturated with a hydrogen atom. In this way, the dihedral angle between the chromophores was kept nearly identical but the larger distance R_{ij} should prevent a significant μm coupling, leaving a dominant μμ coupling (which scales with R_{ij}^{-2}).[7] As expected, the computations resulted in a negative exciton couplet (see the Supporting Information), that is, opposite to the results of the full TDDFT calculations on the intact dimer and in keeping with ECM expectations.

Although the BODIPY chromophore is well known, the chiroptical properties of its chiral derivatives and dimers have been almost neglected. Our investigations show that the uncommonly high magnetic transition dipole moment of the first π–π* excited state of the chromophore has consequences on the ECD of the dimeric BODIPYs. Due to the strong magnetic dipoles and their vicinity in the 1,1′- and the 3,3′-coupled dimers, the straightforward ECM cannot be used to determine the AC of these dimers. This finding is not expected to be unique to BODIPYs. All chromophores with effective C_{2v} symmetry (like BODIPY) have B_1/B_2 transitions which are both electric- and magnetic-dipole allowed. Therefore, the occurrence of strong magnetic transition dipoles in π–π* transitions should be checked for further exciton-coupled systems, including first of all bisphenanthrenes and distorted multiporphyrins.

Received: August 20, 2014

Keywords: BODIPY · chiral resolution · circular dichroism · density functional calculations · exciton chirality method

[1] A. Treibs, F.-H. Kreuzer, *Liebigs Ann. Chem.* **1968**, *718*, 208–223.

[2] G. Ulrich, R. Ziessel, A. Harriman, *Angew. Chem. Int. Ed.* **2008**, *47*, 1184–1201; *Angew. Chem.* **2008**, *120*, 1202–1219.

[3] a) S. Chibani, B. Le Guennic, A. Charaf-Eddin, A. D. Laurent, D. Jacquemin, *Chem. Sci.* **2013**, *4*, 1950–1963; b) B. Le Guennic, O. Maury, D. Jacquemin, *Phys. Chem. Chem. Phys.* **2012**, *14*, 157–164; c) J. L. Jin, S. X. Wu, Y. Geng, S. Y. Yang, G. C. Yang, J. Wu, S. Muhammad, Y. Liao, Z. M. Su, L. Z. Hao, *Int. J. Quantum Chem.* **2012**, *112*, 440–452; d) S. Chibani, B. Le Guennic, A. Charaf-Eddin, O. Maury, C. Andraud, D. Jacquemin, *J. Chem. Theory Comput.* **2012**, *8*, 3303–3313.

[4] a) A. Gossauer, F. Fehr, F. Nydegger, H. Stöckli-Evans, *J. Am. Chem. Soc.* **1997**, *119*, 1599–1608; b) A. Gossauer, F. Nydegger, H. Kim, A. Burghart, M. B. Welch, J. Reibenspies, K. Burgess, *Chem. Commun.* **1999**, 1889–1890; c) T. Kiss, R. Sleziak, H. Stöckli-Evans, *J. Am. Chem. Soc.* **2004**, *126*, 1772–1780; d) A. Haefele, C. Zedde, P. Retailleau, G. Ulrich, R. Ziessel, *Org. Lett.* **2010**, *12*, 1672–1675; e) R. I. Lerrick, T. P. L. Winstanley, K. Haggerty, C. Wills, W. Clegg, R. W. Harrington, P. Bultinck, W. Herrebout, A. C. Benniston, M. J. Hall, *Chem. Commun.* **2014**, *50*, 4714–4716.

[5] a) P. Bonaccorsi, M. C. Aversa, A. Barattucci, T. Papalia, F. Puntoriero, S. Campagna, *Chem. Commun.* **2012**, *48*, 10550–10552; b) H. Xi, C.-X. Yuan, Y.-X. Li, Y. Liu, X.-T. Tao, *CrystEngComm* **2012**, *14*, 2087–2093.

[6] a) G. Beer, C. Niederalt, S. Grimme, J. Daub, *Angew. Chem. Int. Ed.* **2000**, *39*, 3252–3255; *Angew. Chem.* **2000**, *112*, 3385–3388; b) G. Beer, K. Rurack, J. Daub, *Chem. Commun.* **2001**, 1138–1139; c) Y. Wu, X. Mao, X. Ma, X. Huang, Y. Cheng, C. Zhu, *Macromol. Chem. Phys.* **2012**, *213*, 2238–2245.

[7] *Comprehensive Chiroptical Spectroscopy* (Eds.: N. Berova, P. L. Polavarapu, K. Nakanishi, R. W. Woody), Wiley, Hoboken, **2012**.

[8] E. M. Sánchez-Carnerero, F. M. Jimenez, B. L. Maroto, A. R. Agarrabeitia, J. Banuelos, T. Arbeloa, I. López-Arbeloa, M. J. Ortiz, S. de La Moya Cerero, *Chem. Commun.* **2013**, *49*, 11641–11643.

[9] a) J. Ahrens, B. Böker, K. Brandhorst, M. Funk, M. Bröring, *Chem. Eur. J.* **2013**, *19*, 11382–11395; b) J. Ahrens, B. Haberlag, A. Scheja, M. Tamm, M. Bröring, *Chem. Eur. J.* **2014**, *20*, 2901–2912.

[10] a) M. Bröring, R. Krüger, S. Link, C. Kleeberg, S. Köhler, X. Xie, B. Ventura, L. Flamigni, *Chem. Eur. J.* **2008**, *14*, 2976–2983; b) B. Ventura, G. Marconi, M. Bröring, R. Krüger, L. Flamigni, *New J. Chem.* **2009**, *33*, 428–438; c) A. B. Nepomnyashchii, M. Bröring, J. Ahrens, A. J. Bard, *J. Am. Chem. Soc.* **2011**, *133*, 19498–19504; d) A. Poirel, A. De Nicola, P. Retailleau, R. Ziessel, *J. Org. Chem.* **2012**, *77*, 7512–7525.

[11] S. F. Mason, R. H. Seal, D. R. Roberts, *Tetrahedron* **1974**, *30*, 1671–1682.

[12] T. Bruhn, A. Schaumlöffel, Y. Hemberger, G. Bringmann, *Chirality* **2013**, *25*, 243–249.

[13] S. Jurinovich, G. Pescitelli, L. Di Bari, B. Mennucci, *Phys. Chem. Chem. Phys.* **2014**, *16*, 16407–16418.

[14] P. L. Polavarapu, *Chirality* **2008**, *20*, 664–672.

[15] S. Jurinovich, C. A. Guido, B. Mennucci, EXAT (Excitonic Analysis Tool), University of Pisa, Italy, **2014**, https://www1.dcci.unipi.it/molecolab/tools/.

[16] a) S. Matile, N. Berova, K. Nakanishi, J. Fleischhauer, R. W. Woody, *J. Am. Chem. Soc.* **1996**, *118*, 5198–5206; b) D. Gargiulo, F. Derguini, N. Berova, K. Nakanishi, N. Harada, *J. Am. Chem. Soc.* **1991**, *113*, 7046–7047; c) J. D. Chisholm, J. Golik, B. Krishnan, J. A. Matson, D. L. Van Vranken, *J. Am. Chem. Soc.* **1999**, *121*, 3801–3802.

[17] a) T. Hattori, K. Sakurai, N. Koike, S. Miyano, H. Goto, F. Ishiya, N. Harada, *J. Am. Chem. Soc.* **1998**, *120*, 9086–9087; b) A. Solladié-Cavallo, C. Marsol, G. Pescitelli, L. Di Bari, P. Salvadori, X. Huang, N. Fujioka, N. Berova, X. Cao, T. B. Freedman, L. A. Nafie, *Eur. J. Org. Chem.* **2002**, 1788–1796; c) T. Furo, T. Mori, T. Wada, Y. Inoue, *J. Am. Chem. Soc.* **2005**, *127*, 8242–8243; d) J. Joy, R. T. Cheriya, K. Nagarajan, A. Shaji, M. Hariharan, *J. Phys. Chem. C* **2013**, *117*, 17927–17939; e) G. Pescitelli, L. Di Bari, *J. Phys. Chem. C* **2014**, published online, DOI: 10.1021/jp505703k.