RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Intramolecular Diels Alder reactions in highly organized imidazolium salts-based ionic liquid crystals

Tien Dat Do[a] **and Andreea R. Schmitzer***[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

This paper describes the development of a new family of ionic liquid crystals based on imidazolium salts and their applications as media for intramolecular Diels Alder reactions. The use of highly organized smectic T phases showed to be an efficient method to obtain the intramolecular Diels Alder product in high yields, without using high dilution conditions. The ionic liquid crystal media can be recycled in an easy procedure and reused up to at least five times, without loss of reactivity and selectivity.

Introduction

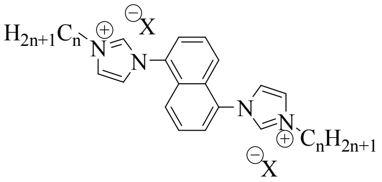
The growing awareness of the use of environmentally benign solvents has led to the increasing importance of ionic liquids as alternative solvents for various organic reactions.[1] Ionic liquids (ILs) represent an interesting class of solvents, as they are liquid at low temperatures, thermically and chemically stable and non-volatile.[2] Ionic liquids had shown significant advantages when used as solvents for organic transformations, in terms of giving similar to higher yields compared to those obtained in traditional organic solvents, as well as a high recyclability.[2,3,4,5] Ionic liquids, by providing an ionic environment, may have a positive effect on reactions possessing polar transition states. The solvent effect is thus more pronounced in ionic liquids and some condensation reactions, as the Diels Alder,[4] Mannich[5] or Friedlander[6] reactions have been conducted successfully in ionic liquids. Imidazolium-based ionic liquids have been shown to enhance the reaction rate and the stereoselectivity of the Diels Alder reaction[4] by hydrogen bonding of the most acidic hydrogen of the imidazolium cation and the carbonyl group of the substrate. However, the slow diffusion rate in ionic liquids and hence the acceleration of the intermolecular reactions result in competitive intermolecular products when ionic liquids are used as solvents for the Diels Alder reaction.[7] A common way to solve this problem is the use of high dilution conditions, preventing the reactant molecules to meet each other and to form intermolecular product. However, this approach requires an important amount of ionic liquids. Therefore, a successful strategy to obtain the intramolecular Diels Alder (IMDA) product in high yields might be to create a certain isolation of the reactant molecules in the reaction mixture by using an organized media.

Liquid crystals (LC) are a class of compounds that can show both unorganized and organized structures depending on the temperature (thermotropic liquid crystals), or the composition of the mixture (lyotropic liquid crystals).[8] The highly organized structure of LC has been showed to affect the outcome of organic reactions performed in LC as reaction media, by interacting with the transition state of the reaction. Leigh *et al.*[9] showed that rod-like organized LC favour the product resulting from a rod-like transition state over the product resulting from a globular transition state. This effect was even more pronounced when the liquid crystal was more organized, by reducing the diffusion rate and the rotation of the substrate molecules.[10] It is reasonable to state that a LC state can isolate molecules dispersed into them and that any isolation effect in obtained the isotropic phases. This means that the isolation of the substrate molecules can be controlled by the temperature.

Imidazolium-based thermotropic and lyotropic ionic liquid crystals (ILCs) combine the self-organization properties of liquid crystals (LC) with the unique solvent properties and ion-conducting properties of imidazolium-based ILs. The properties of ILCs are significantly different from those of conventional liquid crystals[11] and change depending on the molecular architecture of the salts and nature of the counterion used. Herein, we report the synthesis, characterization of new ILCs and their use as solvent for the intramolecular Diels Alder reaction. We demonstrate that the organized structure of the liquid crystalline phase favours the formation of the intramolecular Diels-Alder product and the coordinating properties of the ILC accelerate the reaction rate, compared to a classical LC.

Results and discussion

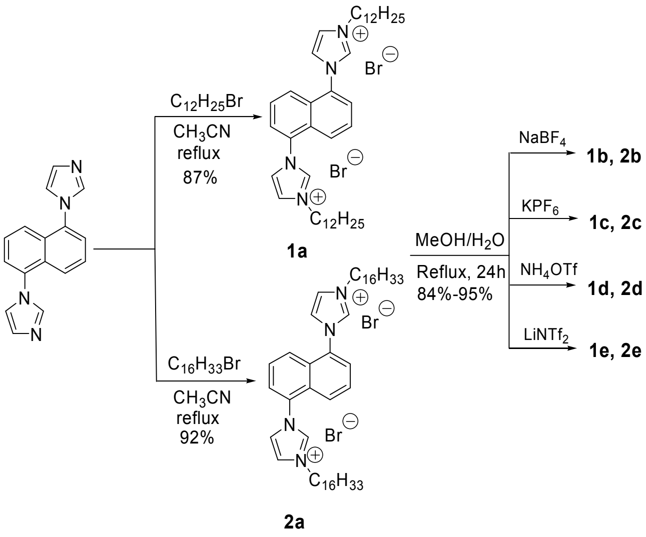
Naphtalene core was previously reported to lower the transition temperature of various LC.[12] Recently, our group demonstrated that dicationic ILCs based on imidazolium salts form a smectic T phase.[13] The transition temperatures being too high to be used as organized solvents for an organic transformation, we decided to replace phenyl core with a naphthalene moiety in order to reduce the anisotropy of the mesogen and to lower the transition temperature of the ILC (Scheme 1).



X = Br n = 12 (**1a**) X = Br n = 16 (**2a**)
X = PF_6 n = 12 (**1b**) X = PF_6 n = 16 (**2b**)
X = OTf n = 12 (**1c**) X = OTf n = 16 (**2c**)
X = BF_4 n = 12 (**1d**) X = BF_4 n = 16 (**2d**)
X = NTf_2 n = 12 (**1e**) X = NTf_2 n = 16 (**2e**)

Scheme 1. Dialkyl (1,5-naphthalene)diimidazolium salts

The synthesis of the dialkyl (1,5-naphthalene)diimidazolium salts from the 1,5-diimidazolenaphtalene is outlined in Scheme 2. All the compounds can be synthesized in grams scale in a four-step procedure from the commercially available 1,5-diaminonaphthalene, by a first diazotization reaction[13] followed by a copper-catalyzed Ullmann reaction following the procedure developed by Taillefer.[14] The alkylation of the diimidazole intermediate by either 1-bromododecane or 1-bromohexadodecane resulted in the desired bromide salts and then different imidazolium salts were obtained by anion metathesis. We decided to use fluorinated anions as NTf_2, OTf, PF_6 and BF_4 which generally result in non-hygroscopic and more acidic ionic liquids.[1,15]



Scheme 2. Synthesis of dialkyl (1,5-naphthalene)diimidazolium salts

Thermophysical properties

The imidazolium salts were first characterized by thermogravimetric analysis in order to study the effect of the counterion and the length of the alkyl chain on the thermal stability of these salts. Results presented in Figure 1 show that the nature of the counterion has a higher influence on the thermal stability of the imidazolium salts than the length of the alkyl chains ($NTf_2^- \cong BF_4^- > TfO^- > Br^- > PF_6^-$). All the salts were stable up to 200°C, but the NTf_2 salts were the most stable ones, up to 250°C.

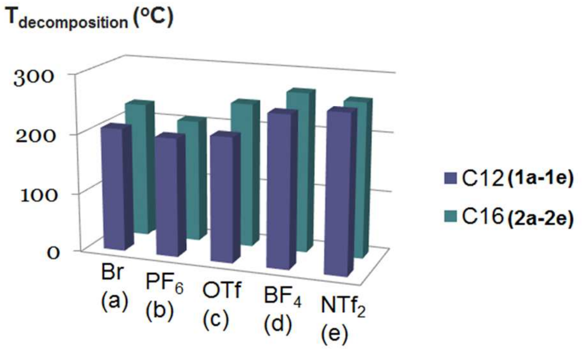


Figure 1. Decomposition temperatures (based on 1% weight loss) of dialkyl (1,5-naphthalene)diimidazolium salts

Liquid crystal properties

For all the compounds, their mesomorphic properties and phase transition temperatures were investigated by differential scanning calorimetry (DSC), polarizing optical microscopy (POM), and powder X-ray diffractometry (PXRD). To avoid hydration of the imidazolium salts, all the compounds were dried under vacuum before the PXRD and DSC analyses. Only the NTf_2 salts showed a liquid - isotropic transition (Figure 2), also confirmed by polarized optical microscope (POM).

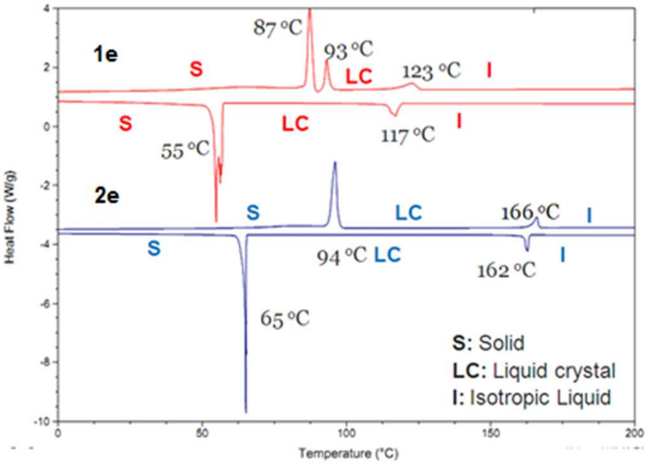


Figure 2. DSC traces of **1e** and **2e** (second heating/cooling cycle).

The phase transition temperatures and the corresponding enthalpy changes derived for compounds **1e** and **2e** in both heating and cooling cycles are shown in Table 1. Both compounds **1e** and **2e** showed lancet-like texture (Figure 3). The lancet-like texture was already reported in highly ordered liquid crystalline phase, for example smectic E or smectic T phases.[16] In the PXRD patterns of both NTf_2 salts, equidistant peaks were observed, showing the lamellar structure of an ordered phase. In the wide angles region, the broad hallow band was not observed, but sharp Bragg reflections appeared, indicative of an ordered arrangement within a smectic T phase for both compounds **1e** and **2e**. The unit cell parameter a of the square lattice was 10.6 Å for both compounds **1e** and **2e** compounds, but the thickness of the layer was 27.7 Å for **1e** and 31.9 Å for **2e** respectively, supporting the hypothesis of a tetragonal structure of a smectic T phase. The value of 10.6 Å for parameter *a* is in agreement with the size of NTf_2 anion (6.6 Å). However, the thickness of the layer is smaller than the estimated molecular length (8.4 Å). This observation suggests a certain degree of interdigitation between two adjacent molecules.

Table 1. Phase transition temperatures and corresponding enthalpies ΔH determined from 1st cooling and 2nd heating DSC thermograms

Compounds on heating	T/°C (Cr1→Cr2) ($\Delta H/J.g^{-1}$)	T/°C (Cr2→LC) ($\Delta H/J.g^{-1}$)	T/°C (LC→I) ($\Delta H/J.g^{-1}$)
1e	87 (33.4)	93 (11.6)	123 (7.5)
2e	-	94 (58.3)	166 (8.2)
Compounds on cooling	T/°C (Cr1→Cr2) (ΔH/J.g-1)	T/°C (Cr2→LC) ($\Delta H/J.g^{-1}$)	T/°C (LC→I) ($\Delta H/J.g^{-1}$)
1e	55	57 (57.8)	117 (8.1)
2e	-	65 (80.0)	162 (7.9)

[a] Abbreviations: Cr1, Cr2 for the solid crystalline phases (S in the DSC traces), LC for liquid crystal phase, and I for isotropic phases.

ILCs as solvents for the intramolecular Diels Alder reaction

IMDA reaction is a very important reaction in organic synthesis, as many C-C bonds can be formed at the same time and it can be used as a tool to synthesize cyclic compounds[17]. Moreover, substrates belonging to the ester-tethered 1,3,9-decatriene system have low reactivity in the IMDA reaction, because their *cis* conformation is not favored due to *trans*-annular and non-bonding electron pair interactions (Scheme 3).[9]

As an alternative to the previously described high dilution conditions in ILs for the IMDA reaction[7], we decided to use ILCs **1e** and **2e** as solvent, hypothesising that the ILCs in the LC phase will be able to disperse the substrate molecules and will favor the intramolecular reaction (Figure 4).

We decided to perform the IMDA of various substrates at various concentrations in both traditional *bis*(trifluoromethane sulfonyl)imide 1-butyl-3-methylimidazolium [Bmim][NTf_2] ionic liquid and **1e,** as it possess a lower transition temperature than **2e.** The same procedure was applied when the traditional ionic liquid was used as solvent.

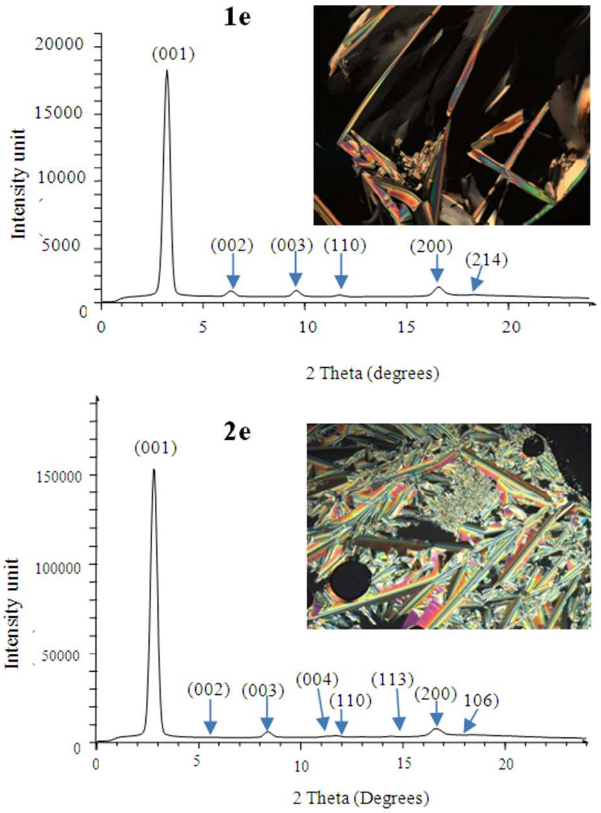


Figure 3. PXRD pattern and POM image of **1e** and **2e** at 90°C.

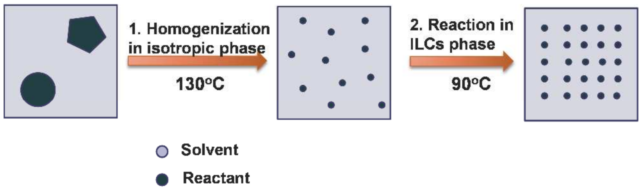
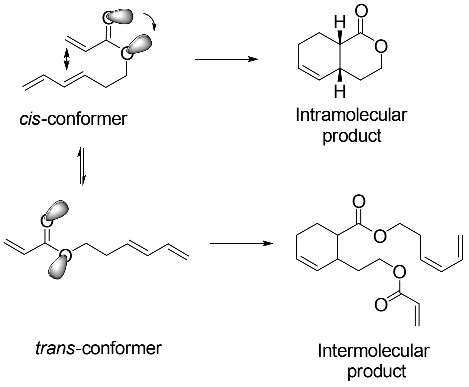


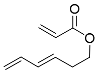
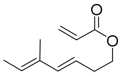
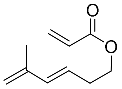
Figure 4. Schematic representation of the dispersion of the substrate in the LC phase



Scheme 3. Intermolecular and Intramolecular Diels Alder products for the ester-tethered 1,3,9-decatriene substrate

As shown in Table 2, considerably less intermolecular product was obtained in the ILC **1e**, compared to the traditional IL, even in high concentration conditions, for all the tested substrates. The best results in terms of selectivity were obtained for the non-substituted substrates, where no intermolecular product was observed at 1:8, 1:16 and 1:32 substrate:ILC ratios. For substrates presenting a substituent on the diene moiety, the intramolecular product is the major product obtained and the intermolecular product was obtained also at less than 5%. However, all the substrates possessing a substituent to the dienophile moiety showed no reactivity in both IL and ILC, where no conversion was obtained even after 36 hours. The presence of a substituent on the dienophile moiety may cause steric hindrance in the transition state, preventing the reaction to take place.

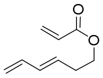
Table 2. Diels Alder reactions in various dilution conditions

Ratio Substrate: Solvent	Substrate	IL [Bmim][NTf$_2$] Isolated yield (%) Inter	IL [Bmim][NTf$_2$] Isolated yield (%) Intra*	ILC (**1e**) Isolated yield (%) Inter	ILC (**1e**) Isolated yield (%) Intra*
1:4		14	22	10	58
1:8		16	41	1	70
1:16		9	63	-	75
1:32		7	69	-	73
1:4		15	54	5	72
1:8		12	48	3	75
1:16		13	53	2	71
1:32		8	68	2	73
1:4		8	52	6	71
1:8		8	57	5	72
1:16		7	54	5	71
1:32		6	63	5	73

*Only the *endo* diastereoisomer of the intramolecular product was observed

The influence of the LC phase, compared to the solid phase was studied by performing the same reaction at different temperatures, under the same concentration (Table 3). It is not surprising that performing the reaction in the solid state (at 50°C) gave lower results in terms of selectivity and reactivity, compared to those obtained in the LC phase.

Table 3. Influence of the solvent organization on the selectivity of the Diels Alder reaction performed at 1:8 substrate:**1e** ratio

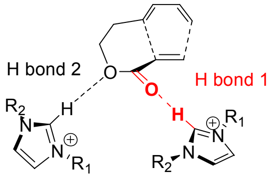
Substrate	Isolated yields (%) Reaction at 50°C Inter	Isolated yields (%) Reaction at 50°C Intra	Isolated yields (%) Reaction at 90°C Inter	Isolated yields (%) Reaction at 90°C Intra
	20	31	1	70

The favoured intramolecular reaction in high concentration conditions may be the result of the presence of the highly organized structure of the smectic T phase around the substrate, preventing two substrate molecules to react and give the intermolecular product.

Table 4 and Figure 5 present data obtained for fully optimized B3LYP/6-31G(d) geometries of *cis* and *trans* 1,3,9-decatriene conformers in the presence of 2 equivalents of IL and ILCs. First, the calculations correctly predict the *endo* selectivity for the IMDA reaction in the presence of both IL and ILCs. The second conclusion that can be drawn when looking at the energy difference between the *cis* and *trans* conformers, is that the cis conformation is favored in the presence of the ILCs. The π-π between the diene unit and the naphthalene core, as well as the additional hydrogen bond observed in this case may be responsible for the higher specificity of the IMDA reactive conformer.

The Diels Alder reactions performed in ILCs gave higher conversions compared to the ones performed in traditional ionic liquids. This increased reactivity is probably due to the more acidic H-2 of the imidazolium cation in ILCs, due to its conjugation with the naphthalene ring (Table 4). By hydrogen bonding the carbonyl group of the substrate, the imidazolium cation of the ILC may also lower the energy of the transition state.

Table 4. B3LYP/6-31G(d) energy difference between conformers *cis* and *trans* and length of hydrogen bonds of the *cis* conformer with IL and ILC



R_1 and R_2 represent the IL or ILCs substituents

ΔE (*cis-trans*) (kcal/mol) IL	ΔE (*cis-trans*) (kcal/mol) ILC	Hydrogen bond 1 (Å) IL	Hydrogen bond 1 (Å) ILC	Hydrogen bond 2 (Å) IL	Hydrogen bond 2 (Å) ILC
2.38	5.01	1.85	1.35	none	1.61

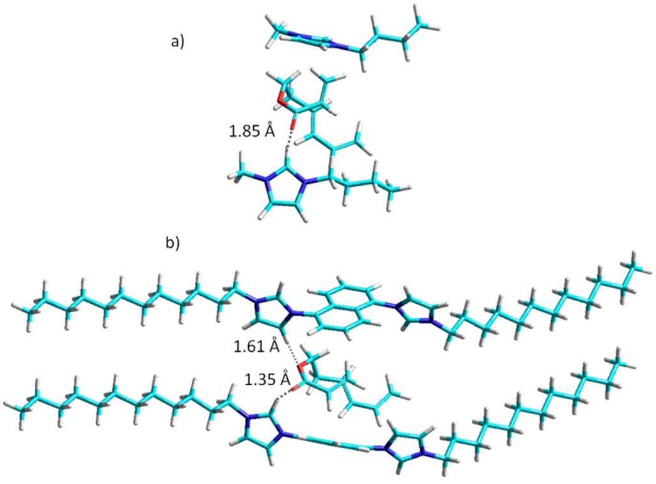
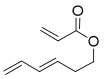


Figure 5. Optimized geometries of the 1,3,9-decatriene substrate with 2 equivalents of a) IL or b) ILCs (the NTf$_2$ anions are not shown for clarity)

Recyclability of the ILC

After the reaction was completed, the reaction mixture was extracted with diethyl ether and the ILC was directly reused for further reactions. As shown in Table 5, the ILC can be reused up to at least 5 catalytic runs, without loss of reactivity and selectivity.

Table 5. Recycling of **1e** after each Diels Alder reaction performed at 1:8 substrate:**1e** ratio (reaction performed at 90°C for 18 h)

Substrate	Catalytic run	Isolated yields (%)	
		Inter	Intra
	1	1	72
	2	2	70
	3	1	74
	4	1	74
	5	1	71

Conclusions

In conclusion, we synthesized and characterized new family of imidazolium salts-based ionic liquid crystals which exhibited highly ordered smectic T phase, with transition temperatures below 100^{o}C. The use of these ILCs as reaction media in the Diels Alder reaction allowed the formation of the intramolecular products in high concentration conditions. Recycling studies showed that the ionic liquid crystals were still active after at least five catalytic runs without loss of reactivity or selectivity. These new ILCs may be useful as reaction media for different macrocyclization reactions, which may broaden the scope of this methodology to other organic reactions.

Notes and references

[a] *Département de Chimie, Université de Montréal, 2900 Édouard Montpetit CP6128 Succursale centre ville, Montréal, H3C3J7, Qc, Canada. *E-mail:* ar.schmitzer@umontreal.ca

† Electronic Supplementary Information (ESI) available: general and analytical methods, synthesis and characterization of the compounds, TGA curves and molecular modelling details. See DOI: 10.1039/b000000x/

‡ We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds Québécois pour la Recherche, la Nature et les Technologies (FQRNT), the Centre in Green Chemistry and Catalysis and the Université de Montréal for financial support. We thank S. Essiembre and P. Ménard-Tremblay for assistance in PXRD and POM studies.

1 S. Wasserscheid, T. Welton *Ionic Liquids in Synthesis*, Second Edition, Wiley VCH, Weiheim 2008

2 (a) T. Welton, *Chem Rev* 1999, **99**, 2071; (b) J. P. Hallet, T. Welton, *Chem Rev*, 2011, **111**, 3508.

3 Mohammad A., Inamuddine *Green Chemistry II : Properties and Applications of Ionic Liquids*, Springer, **2012**.

4 (a) C. E. Song, W. H. Shim, E. J. Roh, S. Lee, J. H. Choi *Chem. Commun.*, 2001, 1122; (b) Aggarwal, A. *Green Chem.* 2002, **4**, 517

5 N. S. Chowdari, D. B. Ramacharie, C. F. Barbas, *Synlett.*, 2003, **12**, 1906.

6 S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Org. Chem.*, 2003, **68**, 9371.

7 H. Yanai; H. Ogura, T. Taguchi, *Org. Biomol. Chem.*, 2009, **7**, 3657.

8 P. J. Collings. M. Hird *Introduction to Liquid Crystals,* Taylor and Francis, 2002.

9 W. Leigh, D. S. Mitchell. *J. Am. Chem. Soc.,* 1992, **114** (13), 5005.

10 (a) K. M. Lee, Y. T. Lee, J. B. Lin, *J. Mater. Chem. 2003*, **13**, 1079; (b) J. De Roche, C. M. Gordon, C. T. Imrie, M. D. Ingram, A. R. Ingram, A. R. Kenedy, F. LoCelso, A. Triolo, *Chem. Mater.* 2003, **15**, 2003; (c) S. Kumar, S. Kumar, *Tetrahedron Lett.* 2005, **46**, 2607; (d) J. Motoyagani, T. Fukushima, T. Aida, *Chem. Commun.,* 2005, 101; (e) J. M. Suisse, S. Bellemin-Laponnaz, L. Douce, A. Maisse-François, R. Welter, *Tetrahedron Lett.* 2005, **46**, 4303. (f) K. Binnemans, *Chem. Rev.* 2005, **105**, 4148.

11 W. Dobbs, L. Douce, L. Allouche, A. Louati, F. Malbosc, R. Welter, *New J. Chem.* 2006, **30**, 528.

12 a) C. Tschierske *Liquid Crystals: Materials Design and Self-Assembly* Springer, **2012**. b) M. Lehmann, M. Jahr, J. Gutmann *J. Mater. Chem.*, 2008,**18**, 2995.

13 N. Noujeim, S. Samsam, L. Eberlin, S. H. Sanon, D. Rochefort, A. R. Rochefort, *Soft Mater.*, 2012, **8**, 10914.

14 H.-J. Cristau, P. P. Cellier, J.-F. Spindler, M. Taillefer, *Chem. Eur. J.,* 2004, **10**, 5607

15. S. Sowmiah, V. Srinivasadesikan, M.-C. Tseng, Y.-H. Chu, *Molecules*, 2009, **14**, 3780.

16 (a) K. Goossens, K. Lava, P. Nockemann, K. Van Heck, L. Van Meervelt, C. Gorller-Walrand, K. Binnemans, T. Cardinaels, *Chem. Eur. J.,* 2009, **15**, 656; (b) E. Alami, H. Levy, R. Zana, P. Weber, Skoulios A., *Liquid Crystals,* 1993, **13** (2), 201.

17 K.-I. Takao, R. Munakata, K.-I. Tadano, *Chem. Rev.*, 2005, **105**, 477.