Dyes and Pigments 112 (2015) 274–279

Contents lists available at ScienceDirect

Dyes and Pigments

journal homepage: www.elsevier.com/locate/dyepig

Facile and environmentally friendly halogenation of BODIPYs in deep eutectic solvent

Liang Wang*, Kai-qiang Zhu, Qun Chen, Ming-yang He*

School of Petrochemical Engineering and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou, 213164, PR China

ARTICLE INFO

Article history:
Received 20 May 2014
Received in revised form
16 July 2014
Accepted 17 July 2014
Available online 28 July 2014

Keywords:
Deep eutectic solvent
Hexafluoroisopropanol
Halogenation
Boron dipyrromethene
Green chemistry
Fluorescent dye

ABSTRACT

A deep eutectic solvent based on choline chloride and 1,1,1,3,3,3-hexafluoro-2-propanol was prepared. This deep eutectic solvent was used as the reaction medium for halogenation of boron dipyrromethene in the presence of *N*-halosuccinimide, which delivered the corresponding products in good to excellent yields (79–94%) in short reaction time (usually within 30 min). Moreover, this deep eutectic solvent could be easily prepared, recovered and reused for several runs without significant loss in the yields.

1. Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-s-indacenes (BODIPYs) have received much attention due to their unique properties including high fluorescence quantum yields (Φ_f), large molar absorption coefficients (ε), excellent thermal and photochemical stabilities [1–3]. Recently, much effort has been spent on the decoration of the BODIPY scaffold with functional groups to modify their photophysical properties, making them excellent fluorophores in various fields [4–6]. Among them, halogenated BODIPYs are of great interest since they are useful precursors for further functionalization. For examples, 3,5-dihalogenated BODIPYs (Fig. 1A) are generally modified via S_NAr reactions and metal-catalyzed cross-coupling reactions to provide more complex BODIPY derivatives [7–10]. The 2,6-halogenated BODIPYs (Fig. 1B) are also effective sensitizers for photodynamic therapy (PDT) [11,12] and photocatalysts [13–15].

Direct electrophilic halogenation of BODIPYs is well-documented in literature. Using bromination as example, a series of reaction systems including *N*-bromosuccinimide (NBS) [16], bromine [17], NBS-AIBN [12] and $CuBr_2$ [18] has been developed. However, prolonged reaction time, relatively lower yields as well as toxic reagents or solvents are still the issues to be addressed.

More recently, deep eutectic solvents (DESs) have invoked great interest as green solvents or catalysts in organic reactions [19–22]. They are mainly prepared by combining a quaternary ammonium salt with a hydrogen-bond donor. The unique properties such as ready available, biodegradable, non-toxic, inexpensive and reusable make them more advantageous than the conventional solvents. On the other hand, it is well known that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) exhibits high hydrogen bonding donor ability, low nucleophilicity and high ionizing power. Its utilization in organic transformations has also been well-documented [23–26]. We believe that HFIP can be used to form a deep eutectic solvent with a quaternary ammonium salt. Also, HFIP also can activate the *N*-halosuccinimide via hydrogen bonding. Herein, we report the preparation of a new DES (ChCl/HFIP) and halogenation reaction of BODIPYs in such DES (Scheme 1).

2. Experimental

2.1. Method and apparatus

All reagents were obtained from local commercial suppliers and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance III 500-MHz spectrometer.

* Corresponding authors. Tel.: +86 519 86330263; fax: +86 519 86330251.
E-mail addresses: lwcczu@126.com (L. Wang), hemingyangjpu@yahoo.com (M.-y. He).

http://dx.doi.org/10.1016/j.dyepig.2014.07.024
0143-7208/

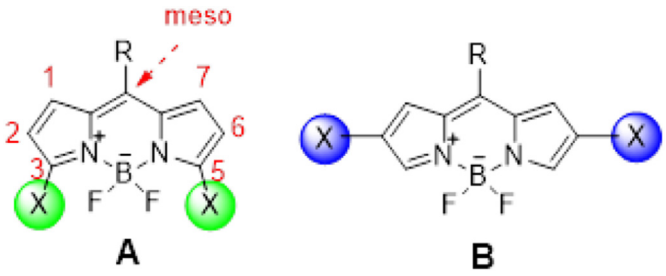


Fig. 1. 3,5- and 2,6-dihalogenated BODIPYs.

NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants J are given in Hz. Melting points (m.p.) are determined with a MPA 100 apparatus and are not corrected. Mass spectra (EI) were measured with Jeol JMS-DX300 and Thermo Fisher LCQ instruments. Elemental analyses were obtained using a Perkin–Elmer EA2400II analyzer.

2.2. Preparation of ChCl/HFIP

Choline chloride (139.6 g, 100 mmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (25.2 g, 150 mmol) were placed in a round bottom flask and stirred at 50 °C. After 3 h, a homogenous colorless liquid formed, which was used directly for the reactions without purification.

2.3. General procedures for halogenation of BODIPYs

A mixture of the BODIPY **1** (0.2 mmol) and either NBS or NIS (0.48 mmol) in ChCl/HFIP (2 mL) was stirred at room temperature for a certain time (usually < 30 min) according to the TLC (EtOAc/petroleum, 1:5). After reaction, the mixture was extracted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was further purified using column chromatography (EtOAc/petroleum ether or CH_2Cl_2/hexane) to afford either the bromo-products **2** or the iodo-products **3**. The ChCl/HFIP, which was insoluble in CH_2Cl_2, was readily recovered by evaporation of the water and reused for the next run. All the products were known compounds and were characterized by comparison with authentic samples.

2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (2a): red solid; m.p. 228–232 °C (229–231 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 7.52–7.53 (m, 5H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.9, 142.1, 140.6, 134.4, 130.4, 129.5, 129.4, 127.8, 111.8, 13.6.

2,6-Dibromo-4,4-difluoro-8-(4-methoxyphenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2b): red solid; m.p. 238–240 °C (236–238 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 6H, CH_3), 2.62 (s, 6H, CH_3), 3.91 (s, 3H, OCH_3), 7.06 (d, J = 8.65 Hz, 2H, ArH), 7.16 (d, J = 8.65 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6, 153.7, 142.3, 140.6, 130.9, 130.8, 129.1, 128.8, 126.3, 114.8, 111.7, 55.4, 13.9, 13.7.

2,6-Dibromo-4,4-difluoro-8-(4-chlorophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2c): red solid; m.p. 208–210 °C (212–214 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 7.21–7.23 (d, J = 10.0 Hz, 2H, ArH), 7.52–7.54 (d, J = 10.0 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 140.4, 140.3, 135.9, 132.8, 130.3, 129.8, 129.4, 128.6, 112.1, 13.9, 13.7.

2,6-Dibromo-4,4-difluoro-8-(4-nitrophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2d): red solid; m.p. > 250 °C (>300 °C) [18]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 7.55 (d, J = 8.6 Hz, 2H, ArH), 8.44 (d, J = 8.6 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 148.7, 141.2, 140.0, 138.6, 129.6, 124.6, 112.5, 14.0, 13.8.

2,6-Dibromo-4,4-difluoro-8-(3,5-dinitrophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2e): red solid; m.p. > 250 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 8.56 (s, 2H, ArH), 9.23 (s, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 149.0, 141.8, 138.8, 134.5, 130.7, 129.2, 122.6, 119.4, 15.4, 14.8. EI-MS: m/z = 572 $[M]^+$. Anal. Calcd for $C_{19}H_{15}BBr_2F_2N_4O_4$: C, 39.90; H, 2.64; N, 9.80. Found: C, 39.87; H, 2.70; N, 9.76.

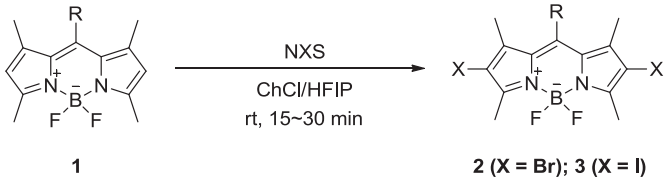
2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-methyl-4-bora-3a,4a-diaza-s-indacene (2f): red solid; m.p. 221–223 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 6H, CH_3), 2.57 (s, 6H, CH_3), 2.62 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.2, 141.9, 138.4, 29.7, 17.4, 16.4, 13.6. EI-MS: m/z = 420 $[M]^+$. Anal. Calcd for $C_{14}H_{15}BBr_2F_2N_2$: C, 40.05; H, 3.60; N, 6.67. Found: C, 40.11; H, 3.52; N, 6.70.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-pentyl-4-bora-3a,4a-diaza-s-indacene (2g): red solid; m.p. 216–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.36–1.66 (m, 8H), 2.44 (s, 6H, CH_3), 2.57 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.3, 147.3, 137.7, 130.5, 112.0, 32.5, 31.5, 29.0, 22.5, 15.5, 14.0, 13.7. EI-MS: m/z = 476 $[M]^+$. Anal. Calcd for $C_{18}H_{23}BBr_2F_2N_2$: C, 45.42; H, 4.87; N, 5.89. Found: C, 45.40; H, 4.91; N, 5.87.

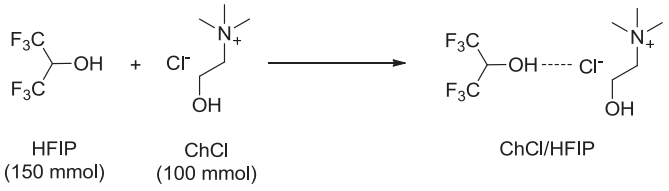
2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-undecyl-4-bora-3a,4a-diaza-s-indacene (2h): red solid; m.p. 202–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88–0.91 (t, 3H, CH_3), 1.22–1.65 (m, 18H, CH_2), 2.44 (s, 6H, CH_3), 2.57 (s, 6H, CH_3), 3.70–3.74 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.3, 147.3, 137.7, 130.5, 112.0, 31.8, 31.7, 30.3, 29.0, 22.6, 18.4, 15.5, 14.1, 13.7. EI-MS: m/z = 560 $[M]^+$. Anal. Calcd for $C_{24}H_{35}BBr_2F_2N_2$: C, 51.46; H, 6.30; N, 5.00. Found: C, 51.47; H, 6.25; N, 5.02.

2,6-Dibromo-4,4-difluoro-1,3,5,7-tetramethyl-8-ethoxycarbonyl-4-bora-3a,4a-diaza-s-indacene (2i): red solid; m.p. > 250 °C; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 1.42–1.45(t, 3H), 2.13(s, 6H), 2.56 (s, 6H), δ4.43–4.48 (q, 2H); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 164.5, 154.6, 135.9, 129.8, 126.9, 122.8, 63.2, 13.8, 12.7, 10.5. EI-MS: m/z = 478 $[M]^+$. Anal. Calcd for $C_{16}H_{17}BBr_2F_2N_2O_2$: C, 40.21; H, 3.59; N, 5.86. Found: C, 40.16; H, 3.62; N, 5.80.

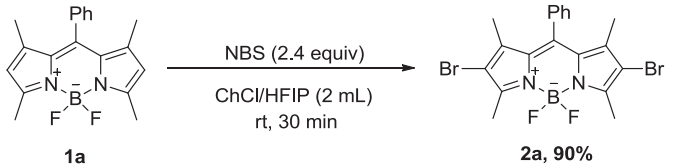
2,6-Dibromo-4,4-difluoro-8-(morpholinomethyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2j): red solid; m.p. 228–231 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.74 (t, 4H, CH_2), 3.76



Scheme 1. 2,6-dihalogenation of BODIPYs in ChCl/HFIP.



Scheme 2. Preparation of ChCl/HFIP.

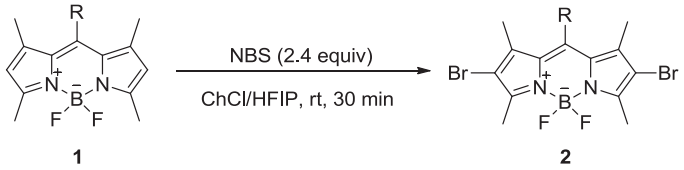


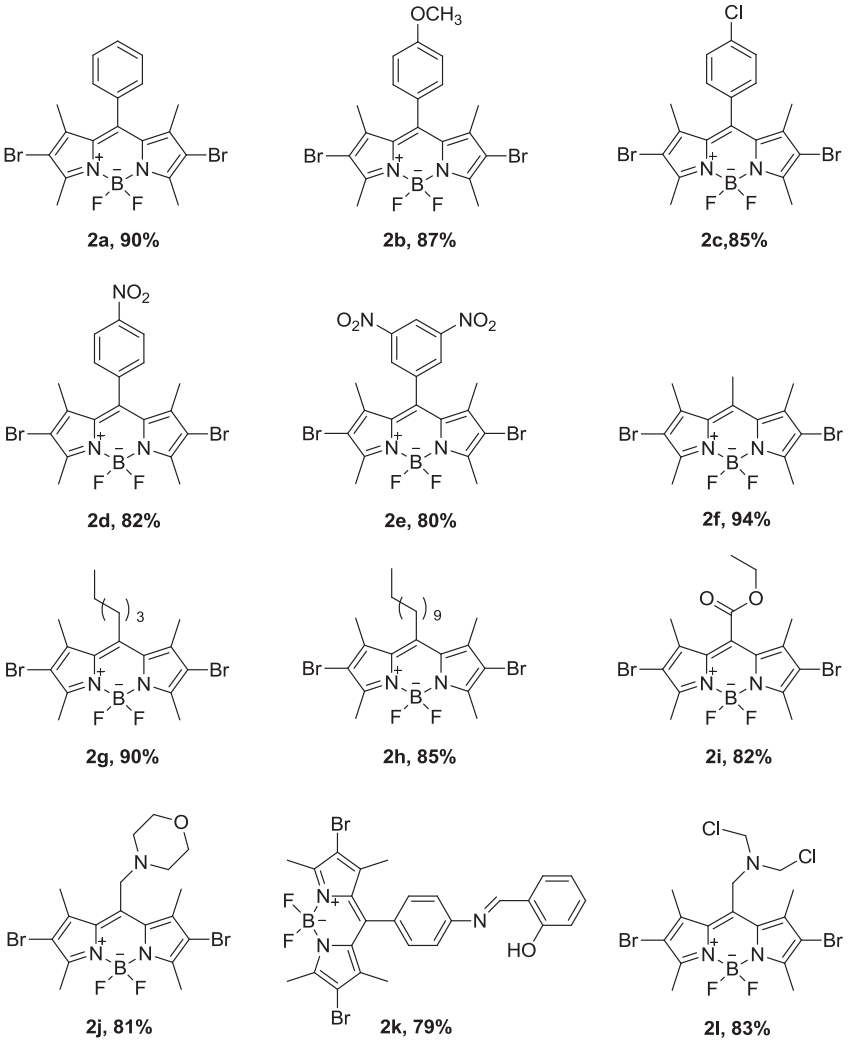
Scheme 3. Model bromination reactions in ChCl/HFIP.

(t, 4H, CH_2), 3.85 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 154.0, 142.2, 142.0, 140.4, 132.4, 131.8, 121.7, 119.7, 67.1, 55.7, 54.1, 17.5, 17.4, 16.5, 14.5. EI-MS: m/z = 505 $[M]^+$. Anal. Calcd for $C_{18}H_{22}BBr_2F_2N_3O$: C, 42.81; H, 4.39; N, 8.32. Found: C, 42.78; H, 3.31; N, 8.35.

2,6-Dibromo-4,4-difluoro-8-(4-((2-hydroxybenzylidene)amino)phenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2k): red solid; m.p. 236–238 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.55 (m, 6H, CH_3), 2.57 (s, 6H, CH_3), 6.96–6.99 (m, 2H, ArH), 7.05–7.44 (m, 6H, ArH), 8.72 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 161.3, 155.7, 149.2, 143.0, 141.0, 133.7, 133.6, 132.5, 131.5, 129.3, 129.0, 122.0, 121.4, 119.2, 119.0, 117.6, 117.4, 115.4, 18.5, 14.6. EI-MS: m/z = 601 $[M]^+$. Anal. Calcd for $C_{26}H_{22}BBr_2F_2N_3O$: C, 51.95; H, 3.69; N, 6.99. Found: C, 51.91; H, 3.65; N, 7.02.

Table 1
Bromonation of BODIPYs.[a]





[a] Reaction conditions: 1 (0.2 mmol), NBS (2.4 equiv), DES (2 mL), 25 °C, 30 min, isolated yields.

2,6-Dibromo-4,4-difluoro-8-((bis(chloromethyl)amino)methyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (2l): red solid; m.p. 217–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.00 (t, 2H, CH_2), 3.56 (t, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 154.5, 142.4, 142.2, 140.4, 132.5, 131.9, 121.9, 119.9, 57.1, 51.9, 42.0, 17.5, 17.4, 16.5, 14.5. EI-MS: m/z = 531 $[M]^+$. Anal. Calcd for $C_{16}H_{18}BBr_2Cl_2F_2N_3$: C, 36.13; H, 3.41; N, 7.90. Found: C, 36.10; H, 3.38; N, 7.84.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (3a): red solid; m.p. 194–196 °C (195–197 °C) [27]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 6H, CH_3), 2.65 (s, 6H, CH_3), 7.52–7.53 (m, 5H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 145.4, 141.4, 134.7, 131.3, 129.5, 129.4, 127.8, 85.7, 16.9.

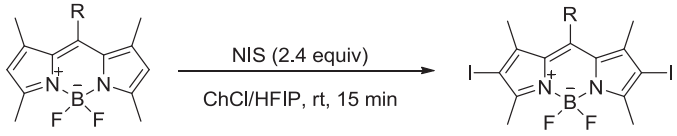
2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-(4-methoxyphenyl)-4-bora-3a,4a-diaza-s-indacene (3b): red solid; m.p. 198–200 °C (196–198 °C) [27]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 6H, CH_3), 2.62 (s, 6H, CH_3), 3.94(s, 3H, OCH_3) 7.04–7.06 (d, J = 10.0 Hz, 2H, ArH), 7.15–7.17 (d, J = 10.0 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6, 153.7, 142.3, 140.6, 130.9, 130.8, 129.1, 128.8, 126.3, 114.8, 111.7, 55.4, 13.8, 13.6.

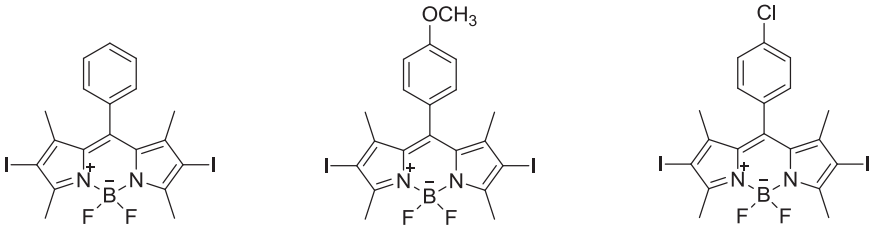
2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-(4-chlorophenyl)-4-bora-3a,4a-diaza-s-indacene (3c): red solid; m.p. 203–204 °C (207–209 °C) [27]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 7.20 (d, J = 10.0 Hz, 2H, ArH), 7.52 (d, J = 10.0 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.2, 145.1, 139.7, 135.8, 133.2, 131.2, 129.8, 129.4, 85.9, 17.2, 16.1.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-(4-nitrophenyl)-4-bora-3a,4a-diaza-s-indacene (3d): red solid; m.p. > 250 °C (>300 °C) [27]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 6H, CH_3), 2.66 (s, 6H, CH_3), 7.54 (d, J = 7.5 Hz, 2H, ArH), 8.42 (d, J = 7.5 Hz, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1, 148.6, 141.7, 141.6, 138.1, 129.5, 124.7, 114.0, 14.9, 14.7.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-methyl-4-bora-3a,4a-diaza-s-indacene (3e): purple solid; m.p. 201–203 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 2.62 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 143.0, 141.1, 132.2,

Table 2
Iodonation of BODIPYs.[a]





[a] Reaction conditions: **1** (0.2 mmol), NIS (2.4 equiv), DES (2 mL), 25 °C, 15 min, isolated yields. For product **3i**, 4.8 equivalent of NIS was used.

85.8, 19.8, 17.9, 16.0. EI-MS: m/z = 514 $[M]^+$. Anal. Calcd for $C_{14}H_{15}BF_2I_2N_2$: C, 32.72; H, 2.94; N, 5.45. Found: C, 32.70; H, 2.90; N, 5.48.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-pentyl-4-bora-3a,4a-diaza-s-indacene (3f): red solid; m.p. 193–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93–0.96 (t, 3H, CH_3), 1.23–1.66 (m, 8H, CH_2), 2.43 (s, 6H, CH_3), 2.61 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 142.2, 131.9, 128.7, 86.8, 32.5, 31.5, 29.3, 22.5, 18.5, 16.1, 14.0. EI-MS: m/z = 570 $[M]^+$. Anal. Calcd for $C_{18}H_{23}BF_2I_2N_2$: C, 37.93; H, 4.07; N, 4.91. Found: C, 37.90; H, 4.11; N, 4.95.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-undecyl-4-bora-3a,4a-diaza-s-indacene (3g): red solid; m.p. 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.90 (t, 3H, CH_3), 1.21–1.60 (m, 18H, CH_2), 2.44 (s, 6H, CH_3), 2.60 (s, 6H, CH_3), 3.67–3.72 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 146.5, 142.3, 131.3, 86.4, 31.9, 31.6, 30.3, 29.6, 29.4, 29.3, 22.7, 18.9, 18.3, 16.1, 14.1. EI-MS: m/z = 654 $[M]^+$. Anal. Calcd for $C_{24}H_{35}BF_2I_2N_2$: C, 44.06; H, 5.39; N, 4.28. Found: C, 44.10; H, 5.37; N, 4.33.

2,6-Diiodo-4,4-difluoro-1,3,5,7-tetramethyl-8-ethoxycarbonyl-4-bora-3a,4a-diaza-s-indacene (3h): red solid; m.p. > 250 °C; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 1.44–1.41 (t, 3H, CH_3), 2.16 (s, 6H, CH_3), 2.62 (s, 6H, CH_3), 4.43–4.47(q, 2H, CH_2). ^{13}C NMR(125 MHz, $CDCl_3$): δ = 164.8, 158.8, 128.8, 128.5, 85.5, 63.2, 16.2, 15.3, 13.8. EI-MS: m/z = 572 $[M]^+$. Anal. Calcd for $C_{16}H_{17}BF_2I_2N_2O_2$: C, 33.60; H, 3.00; N, 4.90. Found: C, 33.63; H, 2.96; N, 4.91.

2,2',6,6'-tetraiodo-4,4,4',4'-difluoro-1,1',3,3',5,5',7,7'-octamethyl-4,4´-dibora-3a,3a',4a,4a'-tetraaza-s-indacene (3i): red solid; m.p. > 250 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.14 (s, 6H, CH_3), 2.58 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 138.6, 128.9, 128.5, 127.6, 13.8, 12.2. EI-MS: m/z = 998 $[M]^+$. Anal. Calcd for $C_{26}H_{24}B_2F_4I_4N_4$: C, 31.30; H, 2.42; N, 5.62. Found: C, 31.35; H, 2.37; N, 5.57.

3. Results and discussion

Initially, DES (ChCl/HFIP) was prepared by simple mixing choline chloride with HFIP at 50 °C till a clear solution was obtained (Scheme 2). The ratio of ChCl/HFIP was 1:1.5 as confirmed by NMR analysis. DSC analysis clearly showed that the melting point of ChCl/HFIP was −37.2 °C. Moreover, ChCl/HFIP was very stable and could be easily stored on the shelf without decomposition.

With this DES in hand, we began to investigate the halogenation reaction. Encouragingly, it was found that upon simple mixing of BODIPY **1a** (0.2 mmol) and *N*-bromosuccinimide (NBS, 2.4 equiv) in ChCl/HFIP (2 mL), the reaction proceeded rapidly to provide the corresponding dibromo-BODIPY **2a** in 90% yield within 30 min (Scheme 3). Other choline-based eutectic mixtures such as choline chloride–urea, choline chloride–malonic acid, choline chloride–glycerol and choline chloride- *p*-toluenesulfonic acid were also evaluated for this reaction. However, BODIPY **1a** was not soluble in these DESs, thus only trace amount of products were obtained.

On the basis of above result, the scope of the BODIPYs was examined and the results were summarized in Table 1. Generally, all of the reactions proceeded smoothly to afford the dibromo-BODIPYS (**2a**~**2l**) in good to excellent yields (79–94%). For the *meso*-aryl substituted BODIPYs **1a**~**1e** and those bearing electron-withdrawing groups, such as a nitro group, relatively lower yields were recorded. The *meso*-ethoxycarbonyl substituted BODIPY was less active than the *meso*-alkyl substituted BODIPYs. Other BODIPYs modified with morpholine, schiff base functions and bis(chloromethyl)amine also showed good compatibilities to deliver the products in good yields.

The iodination reaction in the presence of *N*-iodosuccinimide was then examined (Table 2). As seen from the table, the iodination was more active than the bromination. All the substrates reacted with NIS quickly to give the diiodo substituted BODIPYs (**3a**~**3i**) in good to excellent yields within 15 min (82–92%).

One of the most important advantages employing DES as solvent or catalyst is their recyclability. Thus, the recycling experiments were carried out using bromination of BODIPY **1a** as the model reaction. After completion of the reaction, dichloromethane and water were added and the mixture was stirred for five minutes. The dichloromethane layer containing the starting substrate and product was separated. The aqueous medium was then dried under vacuum at 80 °C to recover the DES. Results showed that the DES could be reused several times with only a gradual decrease in the yield (90%, 90%, 88% and 85%).

4. Conclusion

In summary, a facile and environmentally friendly protocol has been developed for dihalogenation of BODIPYs using ChCl/HFIP as solvent and *N*-halosuccinimide as the halogen source. The reaction completed within 15–30 min to afford the dihalogenated BODIPYs in good to excellent yields. Moreover, the DES ChCl/HFIP can be easily recovered and reused for several runs.

Acknowledgments

We gratefully thank the National Natural Science Foundation of China (21302014), the Natural Science Foundation for Colleges and Universities of Jiangsu Province (13KJB150002), the Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110), and ordinary university graduate student research innovation projects of Jiangsu province (No. KYZZ_0303) for financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dyepig.2014.07.024.

References

[1] Ulrich G, Ziessel R, Harriman A. The chemistry of fluorescent bodipy dyes: versatility unsurpassed. Angew Chem Int Ed 2008;47:1184–201.
[2] Boens N, Leen V, Dehaen W. Fluorescent indicators based on BODIPY. Chem Soc Rev 2012;41:1130.
[3] Leen V, Yuan P, Wang L, Boens N, Dehaen W. Synthesis of meso-halogenated BODIPYs and access to meso-substituted analogues. Org Lett 2012;14:6150–3.
[4] Li W, Zhang W, Dong X, Yan L, Qi R, Wang W, et al. Porous heterogeneous organic photocatalyst prepared by HIPE polymerization for oxidation of sulfides under visible light. J Mater Chem 2012;22:17445–8.
[5] Kamkaew A, Burgess K. Double-targeting using a TrkC ligand conjugated to dipyrrometheneboron difluoride (BODIPY) based photodynamic therapy (PDT) agent. J Med Chem 2013;56:7608–14.
[6] Vázquez-Romero A, Kielland N, Arévalo MJ, Preciado S, Mellanby RJ, Feng Y, et al. Multicomponent reactions for de Novo synthesis of BODIPY probes: in vivo imaging of phagocytic macrophages. J Am Chem Soc 2013;135:16018–21.
[7] Baruah M, Qin W, Vallée RAL, Beljonne D, Rohand T, Dehaen W, et al. A highly potassium-selective ratiometric fluorescent indicator based on BODIPY aza-crown ether excitable with visible light. Org Lett 2005;7:4377–80.
[8] Rohand T, Baruah M, Qin W, Boens N, Dehaen W. Functionalisation of fluorescent BODIPY dyes by nucleophilic substitution. Chem Commun 2006:266–8.
[9] Leen V, Braeken E, Luckermans K, Jackers C, Van derAuweraer M, Boens N, et al. A versatile, modular synthesis of monofunctionalized BODIPY dyes. Chem Commun 2009:4515–7.
[10] Leen V, Leemans T, Boens N, Dehaen W. 2- and 3-Monohalogenated BODIPY dyes and their functionalized analogues: synthesis and spectroscopy. Eur J Org Chem 2011:4386–96.
[11] Yogo T, Urano Y, Ishitsuka Y, Maniwa F, Nagano T. Highly efficient and photostable photosensitizer based on BODIPY chromophore. J Am Chem Soc 2005;127:12162–3.
[12] Atilgan S, Ekmekci Z, Dogan AL, Guc D, Akkaya EU. Water soluble distyryl-boradiazaindacenes as efficient photosensitizers for photodynamic therapy. Chem Commun 2006:4398–400.

[13] Adarsh N, Shanmugasundaram M, Avirah RR, Ramaiah D. Aza-BODIPY derivatives: enhanced quantum yields of triplet excited states and the generation of singlet oxygen and their role as facile sustainable photooxygenation catalysts. Chem Eur J 2012;18:12655–62.
[14] Zhang C, Zhao J, Wu S, Wang Z, Wu W, Ma J, et al. Intramolecular RET enhanced visible light-absorbing Bodipy organic triplet photosensitizers and application in photooxidation and triplet–triplet annihilation upconversion. J Am Chem Soc 2013;135:10566–78.
[15] Huang L, Zhao J, Guo S, Zhang C, Ma J. Bodipy derivatives as organic triplet photosensitizers for aerobic photoorganocatalytic oxidative coupling of amines and photooxidation of dihydroxylnaphthalenes. J Org Chem 2013;78:5627–37.
[16] Bonardi L, Ulrich G, Ziessel R. Tailoring the properties of poron–dipyrromethene dyes with acetylenic functions at the 2,6,8 and 4-B substitution positions. Org Lett 2008;10:2183–6.
[17] Goday J, Vives G, Tour JM. Synthesis of highly fluorescent BODIPY-based nanocars. Org Lett 2010;12:1464–7.
[18] Ye JH, Wang G, Huang C, Hu Z, Zhang W, Zhang Y. An efficient and convenient bromination of BODIPY derivatives with copper(II) bromide. Synthesis 2012;44:104–10.
[19] Abbott AP, Harris RC, Ryder K, Agostino CD, Gladden L, Mantle MD. Glycerol eutectics as sustainable solvent systems. Green Chem 2011;13:82–90.
[20] Ruβ C, König B. Low melting mixtures in organic synthesis-an alternative to ionic liquids? Green Chem 2012;14:2969–82.
[21] Zhang Q, De Oliveira Vigier K, Royer S, Jérôme F. Deep eutectic solvents: syntheses, properties and applications. Chem Soc Rev 2012;41:7108–46.
[22] Gu Y, Jérôme F. Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. Chem Soc Rev 2013;42:9550–70.
[23] Khaksar S, Talesh SM. Transition metal-free oxidation of activated alcohols to aldehydes and ketones in 1,1,1,3,3,3-hexafluoro-2-propanol. J Fluor Chem 2012;140:95–8.
[24] Khaksar S, Talesh SM. A simple, efficient and green procedure for the synthesis of bis-indolyl methanes in 1,1,1,3,3,3-hexafluoro-2-propanol. J Fluor Chem 2012;135:87–90.
[25] Ratnikov MO, Tumanov VV, Smit VA. Lewis acid catalyst free electrophilic alkylation of silicon-capped π donors in 1,1,1,3,3,3-hexafluoro-2-propanol. Angew Chem Int Ed 2008;47:9739–42.
[26] Dohi T, Maruyama A, Minamitsuji Y, Takenaga N, Kita Y. First hypervalent iodine(III)-catalyzed C–N bond forming reaction: catalytic spirocyclization of amides to N-fused spirolactams. Chem Commun 2007:1224–6.
[27] Ye J, Hu Z, Wang Y, Zhang W, Zhang Y. A new practical and highly efficient iodination of BODIPY derivatives with hypervalent iodine reagent. Tetrahedron Lett 2012;53:6858–60.