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Nucleophilic Hydroxylation in Water Media Promoted by a Hexaethylene Glycol-Bridged Dicationic Ionic Liquid

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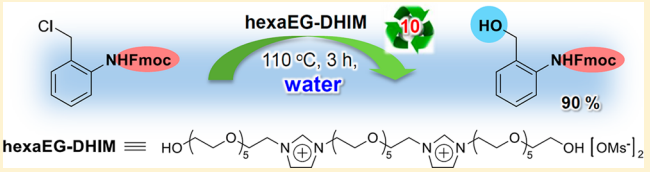
Supporting Information

ABSTRACT: Hexaethylene glycol bis(3-hexaethylene glycol imidazolium) dimesylate ionic liquid (hexaEG-DHIM) was designed and prepared as a highly efficient promoter for the nucleophilic hydroxylation of alkyl halides to the corresponding alcohol products in neat water media. It was observed that hexaEG-DHIM promoter enhanced the nucleophilicity of water significantly in the reaction. In addition, the hexaEG-DHIM could be reused several times without loss of activity. Moreover, the hydroxylation reactions of base-sensitive and/or polar alkyl halide substrates proceeded highly chemoselectively in excellent yields.



Water, the most vital element among the natural resources,[1] is considered a "universal solvent" for most elements and compounds as a result of its unique molecular features.[2] Water has occupied a privileged position in the life sciences due to its numerous attractive properties that include nonhazard, nontoxicity, nonflammability, unique redox-stability, low cost, and environmental compatibility.[3] Because of increasing public concern over the harmful effects of organic solvents on the environment, recent years have witnessed the extensive use of water as a "safer solvent" for various organic transformations. However, the use of water as a solvent is available only for a few chemical reactions due to its high nonspecific reactivity as well as restricted solubility of organic chemicals in water.[4]

Although the incorporation of oxygen nucleophiles into diverse alkyl halide systems is often very difficult, nucleophilic hydroxylation to produce alkyl alcohol compounds is one of the most important substitution reactions in the field of organic chemistry.[5] Generally, water mixed with a strong base or various alkali metal hydroxides in the presence or absence of a phase transfer catalyst (PTC) has been used for the hydroxylation of alkyl halides.[6] However, these methods suffer from the formation of undesired elimination byproducts due to the strongly basic reaction conditions. Polar aprotic solvents, such as DMF, DMSO, and HMPA, are routinely used as reaction media for this type of reaction,[7,8] although major drawbacks such as high boiling point, environmental toxicity, health hazards, and their solubility in both organic and aqueous media restricts their more general application. Reports of ionic liquids (ILs) as the solvent for nucleophilic hydroxylation with water has stimulated a new research direction, which has enabled the more widespread utilization of both water and ILs in eco-friendly organic syntheses.[9] However, the use of ILs in hydroxylation reactions still requires long reaction times and large amounts of ILs, which lowers their cost-effectiveness and introduces purification issues.[9] Therefore, development of new ILs that overcome these drawbacks would represent a significant advancement.

ILs, designed and synthesized as combinations of different cationic and anionic components, have been studied as eco-friendly solvent systems for numerous chemical applications.[10] In the past few years, in parallel with research into monocationic ILs, a new aspect of this area is the development of di-, tri-, and polycationic ILs.[11,12] The interest in these multicationic ionic liquids (MCILs) is mainly due to additional properties such as the opportunity to design structures based on multiple combinations of cations, anions, and linkers to achieve significant properties according to the specific chemical task;[13] high melting points; and thermal stability and volatility higher than that of monocationic ILs.[14] In the framework of our interest in ILs, we recently reported that custom-made oligoethylene glycol substituted monocationic imidazolium salts significantly enhanced the reactivity of alkali metal fluorides in nucleophilic fluorinations compared with conventional ILs (Figure 1).[15] Herein, we designed a more reactive hexaethylene glycol-bridged dicationic imidazolium mesylate

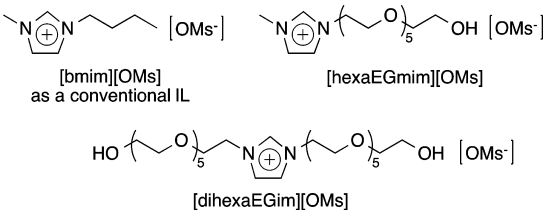


Figure 1. Conventional and custom-made ionic liquids. bmim = 1-*n*-butyl-3-methylimidazolium; hexaEGmim = 1-hexaethylene glycol 3-methylimidazolium; dihexaEGim = 1,3-dihexaethylene glycol imidazolium cation; OMs = mesylate anion.

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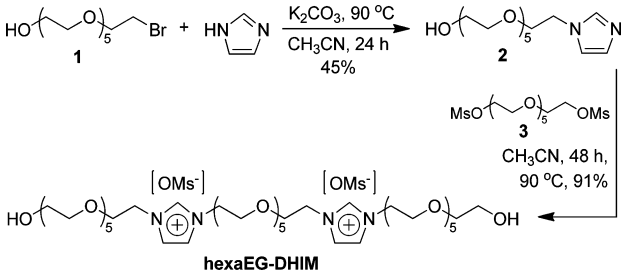
salt (hexaEG-DHIM) for nucleophilic displacement-type reactions by tethering a second imidazolium salt (for a PTC effect) via a hexaethylene glycol (hexaEG) bridge (to provide amphiphilic properties for good interaction between organic molecules and hydrophilic nucleophiles). Interestingly, we found that this hexaEG-DHIM significantly increased the rate of nucleophilic hydroxylation of alkyl halides in water media.

Scheme 1 illustrates the preparation of hexaethylene glycol bis(3-hexaethylene glycol imidazolium) dimesylate (hexaEG-DHIM). An *N*-alkylation reaction of imidazole with hexaethylene glycol bromide (**1**) in the presence of K_2CO_3 in CH_3CN for 24 h afforded hexaethylene glycol imidazole (**2**). Further treatment of **2** (2 equiv) with hexaethylene glycol dimesylate (**3**) for 2 days provided the hexaEG-DHIM in 91% yield as an ionic liquid. The prepared hexaEG-DHIM was characterized by NMR and mass spectroscopy.

Scheme 1. Preparation of HexaEG-DHIM



Our investigation began with an examination of the efficiency of hexaEG-DHIM as a promoter in nucleophilic hydroxylation using water as both the reaction medium and the nucleophile. Initially, we carried out the hydroxylation reaction of 2-(3-bromopropoxy)naphthalene (**4**) as a model compound in the presence of 1.0 equiv of hexaEG-DHIM as a promoter or in the absence of any promoter in water at 110 °C. The comparison study (Figure 2) shows that hexaEG-DHIM was a highly efficient promoter enabling the hydroxylation reaction to proceed significantly faster (affording the desired alcohol product **5a** in 96% yield) than the same reaction without any promoter. These results suggest that hexaEG-DHIM significantly enhanced the nucleophilicity of H_2O due to the possibility of formation of hydrogen bonds between H_2O and hexaEG-DHIM, as well as the PTC effect from the dicationic imidazolium moiety.[15a] In addition, since oxygen in the hexaEG chains can act as Lewis bases, hexaEG-DHIM might reduce the acidity of the reaction medium from in situ generated HBr to prevent the reverse reaction.

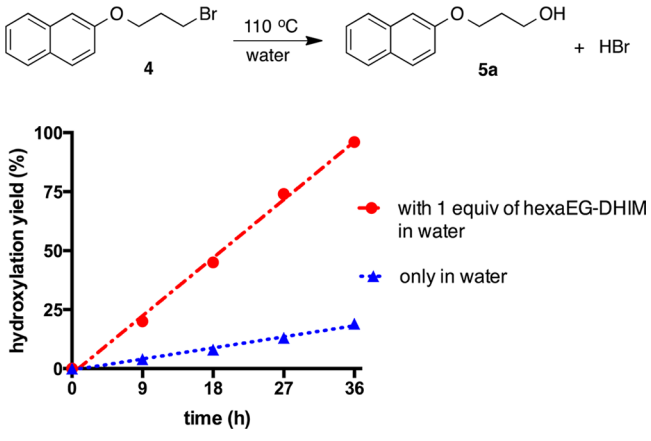
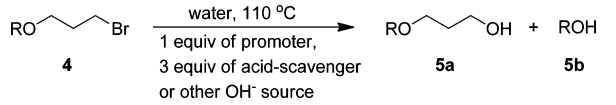


Figure 2. Efficiency of hexaEG-DHIM as a promoter of nucleophilic hydroxylation in water. The quantity of product was determined using ^{1}H NMR spectroscopy.

In light of the above initial results, optimization of the hydroxylation reaction conditions was undertaken, and the results are summarized in Table 1. To increase the solubility of the organic substrate, bromoalkane **4**, in the reaction medium, the hydroxylation was performed in water with an organic cosolvent such as 1,4-dioxane (water/1,4-dioxane = 1:1, v/v) in the presence of hexaEG-DHIM at 110 °C, and this reaction proceeded much faster (within 9 h) compared with the same reaction using only neat water. Next, we attempted to use a weak base to accelerate the reaction rate by scavenging in situ-generated HBr in the hydroxylation reaction. In the organic cosolvent system reaction, a combination of hexaEG-DHIM and $NaHCO_3$ successfully increased the rate of hydroxylation (entry 2). However, the use of $NaHCO_3$ as an acid scavenger did not show satisfactory performance in the hydroxylation using neat water medium (entry 3). Surprisingly, the hydroxylation in neat water using K_2CO_3 as an acid scavenger with hexaEG-DHIM proceeded dramatically faster, reaching completion within only 5 h, and affording the desired product **5a** in excellent yield (98%, entry 4). This result satisfied our aim of developing an environmentally benign hydroxylation procedure. In contrast, bromoalkane **4** was converted to alcohol **5a** in only 19% yield using the same reaction conditions without hexaEG-DHIM (entry 5). To investigate the effect of the hexaEG moiety on promoter efficiency, a variety of ILs

Table 1. Hydroxylation of Bromoalkane 4 in Water under Various Reaction Conditions.[a]



entry	promoter (1 equiv)	acid-scanvenger or other OH^- source (3 equiv)	time (h)	yield[b] (%) 4	5a	5b
1[c]	hexaEG-DHIM	-	9	-	95	5
2[c]	hexaEG-DHIM	$NaHCO_3$	5	-	94	6
3	hexaEG-DHIM	$NaHCO_3$	24	7	88	5
4	hexaEG-DHIM	K_2CO_3	5	-	98 (95)[d]	trace
5	-	K_2CO_3	5	80	19	trace
6	[dihexEGim][OMs]	K_2CO_3	12	-	95	5
7	[hexEGmim][OMs]	K_2CO_3	16	-	94	6
8	[bmim][OMs]	K_2CO_3	48		92	8
9	-	TBAOH	5	69	30	trace
10	18-crown-6	KOH	5	74	23	trace

[a]All reactions were carried out on a 1.0 mmol scale of bromoalkane **4** in 4.0 mL of H_2O in the presence of 1 equiv of promoter and 3 equiv of acid scavenger or other OH^- source at 110 °C. [b]Yields were determined by ^{1}H NMR spectroscopy. [c]These reactions were performed in a solution of 1,4-dioxane (2.0 mL) and H_2O (2.0 mL). [d]Isolated yield. R = 2-naphthyl.

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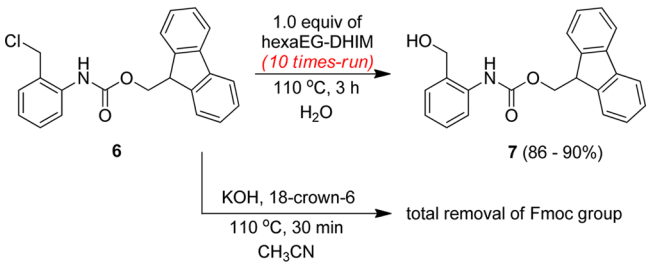
were tested (entries 6–8). Hydroxylation in the presence of monocationic ILs [dihexEGim][OMs] or [hexEGmim][OMs] also furnished the alcohol product **5a** in good yield but required longer reaction times (12 and 16 h for entries 6 and 7, respectively). Accordingly, it was found that the traditional IL [bmim][OMs] was also not a sufficiently effective promoter for this hydroxylation (too long a reaction time: 48 h), furnishing 8% of the dealkylated byproduct **5b** from a hydrolysis side-reaction (entry 8). Moreover, it was observed that the formation of dealkylated byproduct **5b** slightly increased according to the decrease in the number of hexaEG chains in the corresponding IL structure. From these results, it was surmised that the presence of three hexaEGs in a single hexaEG-DHIM molecule might provide an amphiphilic nature and increase hydrogen bonding[16] for good interactions between organic molecules and water, consequently enhancing both the reaction rate and the chemoselectivity. In addition, this hexaEG-DHIM-promoted water media hydroxylation method exhibited much higher efficacy compared with those of conventional PTC methods using TBAOH or the 18-crown-6/KOH complex (entries 9 and 10, respectively).

It is noteworthy that this hexaEG-DHIM-promoted water media hydroxylation method is amenable to the hydroxylation of extremely base-sensitive molecules. For example, Fmoc-2-hydroxymethylaniline (**7**), which has an easily cleaved Fmoc group under basic conditions, was obtained in 90% yield through the water media hydroxylation of *N*-Fmoc-2-chloromethylaniline (**6**) in the presence of hexaEG-DHIM for 3 h, whereas the same reaction using the traditional method (18-crown-6/KOH in CH_3CN) provided only Fmoc-deprotected compounds, as shown in Scheme 2. Furthermore, the

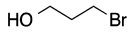
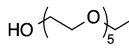
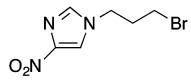
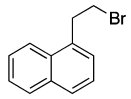
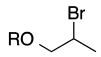
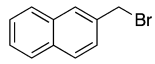
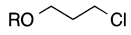
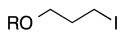
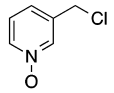
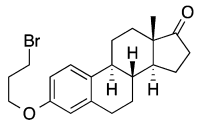
Scheme 2. Chemoselective Water Media Hydroxylation of a Base-Sensitive Substrate 6 with HexaEG-DHIM



recyclability and stability of the promoters after the reaction are essential factors in homogeneous promoter-based organic reactions. In this regard, hexaEG-DHIM could be repeatedly reused (10×-run) in the hydroxylation of **6** without loss of activity or decomposition. In each cycle, the reaction afforded the product **7** in excellent yield (86–90%).

To demonstrate that our protocol is generally applicable to other substrates, we also conducted hexaEG-DHIM-promoted hydroxylation reactions using a range of alkyl halide substrates in water under the same conditions as used for entry 4, shown in Table 1, and the results are summarized in Table 2. Pleasingly, when using polar substrates such as 3-bromopropanol, hexaEG bromide **1**, and nitro-imidazolyl bromide (entries 1–3, respectively), which have relatively good solubility in water, the reactions proceeded at a significantly fast rate and were completed within 1 h to afford the corresponding alcohol products in excellent yields (95–98%). These results indicate that this hydroxylation protocol is useful for the preparation of

Table 2. Water Media Hydroxylation of Various Substrates in the Presence of HexaEG-DHIM.[a]

Entry	Substrate	Time (h)	Temp (°C)	Yield (%)[b]
1		1	100	96
2		1	100	98
3		1	110	95
4		12	110	95
5		9	110	87
6		1	100	97
7		24	110	90
8		10	110	96
9		3	110	96
10		5	100	97

[a]Unless otherwise noted, all reactions were carried out on a 1.0 mmol scale of substrate with 4.0 mL of H_2O in the presence of 1.0 equiv of hexaEG-DHIM and 3.0 equiv of K_2CO_3. [b]Isolated yield. R = naphthyl.

polar alcohol molecules. Generally, incorporation of basic nucleophiles such as hydroxide into haloethyl aromatic molecules is known to be very difficult because of their pronounced tendency to undergo elimination reactions to produce styrenes. However, with this hexaEG-DHIM-promoted aqueous media hydroxylation reaction, a hydroxyl group was successfully incorporated into the bromoethyl aromatic compound in 95% yield, despite a long reaction time due to its low solubility in water (entry 4). Next, we explored hydroxylation of various halide substrates such as secondary alkyl-, benzyl bromide, chloro-, and iodoalkanes, and these reactions provided the corresponding alcohol products in good yields (87–97%, entries 5–8, respectively). α-Hydroxy-3-picoline-*N*-oxide was synthesized in 96% yield from α-chloro-3-picoline-*N*-oxide (entry 9). In a final example (entry 10), the bioactive molecule 3-*O*-(3-bromopropyl)estrone was converted to 3-*O*-(3-hydroxypropyl)estrone in 97% yield under these reaction conditions.

In conclusion, we have designed and prepared a task-specific hexaethylene glycol-bridged dicationic IL (hexaEG-DHIM) that can act as a highly efficient multifunctional organic promoter for nucleophilic hydroxylation in neat water solvent as an alternative to organic solvents. In this reaction, hexaEG-DHIM enhanced the nucleophilicity of water and could be reused several times without loss of activity. In addition, when using polar alkyl halide substrates, the hydroxylation reactions were completed quickly five times compared to using nonpolar

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substrates. These factors are technically attractive for its application in eco-friendly industrial chemical processes. Furthermore, this hexaEG-DHIM-promoted water media hydroxylation protocol allowed reactions of base-sensitive and/or polar alkyl halide substrates to proceed highly chemoselectively to afford the desired alcohol products in excellent yields.

EXPERIMENTAL SECTION

Unless otherwise noted, all reagents and solvents were commercially available. Reaction progress was followed by TLC on 0.25 mm silica gel 60 aluminum sheets containing F-254 indicator. Visualization on TLC was monitored by UV light. Flash chromatography was performed with 230−400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer, and chemical shifts were reported in δ units (ppm) relative to tetramethylsilane. Low- and high-resolution electron impact (EI, 70 eV) spectra were obtained.

17-(1*H*-Imidazol-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-ol (2). Potassium carbonate (916 mg, 6.63 mmol) was added to the solution of imidazole (375 mg, 5.52 mmol) and 17-bromo-3,6,9,12,15-pentaoxaheptadecan-1-ol (**1**, 1.9 g, 5.52 mmol) in CH_3CN (30 mL) at room temperature. The reaction mixture was stirred for 24 h at 90 °C. The reaction mixture was filtered and washed with acetone (75 mL), acetone was concentrated under reduced pressure on rotary evaporator. The crude reaction mixture was extracted with EtOAc (50 mL × 3) dried on sodium sulfate and concentrated under reduced pressure on rotary evaporator. The residue was purified by flash column chromatography (10% MeOH/CH_2Cl_2) to afford 826 mg (0.45 mmol, 45%) of 17-(1*H*-imidazol-1-yl)-3,6,9,12,15-pentaoxaheptadecan-1-ol (**2**) as a colorless thick liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.39−3.44 (m, 18H), 3.52 (t, J = 4.8 Hz, 2H), 3.55 (t, J = 5.4 Hz, 2H), 3.93 (t, J = 4.8 Hz, 2H), 4.28 (bs, 1H), 6.80 (s, 1H), 6.83 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 47.0, 61.1, 69.5, 70.2, 70.4, 70.5, 72.6, 119.5, 128.8, 137.5; MS (EI) m/z 332 (M^+); HRMS (FAB TOF) calcd for $C_{15}H_{29}N_2O_6$ (M^+ + H) 333.2026, found 333.2028.

Hexaethylene Glycol Bis(3-hexaethylene glycol imidazolium) Dimesylate (hexaEG-DHIM). Hexaethylene glycol dimesylate (**3**) (0.66 g, 1.50 mmol) was added dropwise to the solution of **2** (1.0 g, 3.01 mmol) in CH_3CN (25 mL). The reaction mixture was stirred at 90 °C for 24 h and evaporated under reduced pressure to remove CH_3CN. The residue was washed repeatedly with diethyl ether (10 mL × 7) and dried under high vacuum overnight at room temperature to afford 1.50 g (0.91 mmol, 91%) of hexaEG-DHIM as a light yellow thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 6H), 3.50−3.65 (m, 60H), 3.81 (t, J = 6.2 Hz, 6H), 4.42 (t, J = 6.2 Hz, 6H), 7.58 (d, J = 8.0 Hz, 4H), 9.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 49.4, 61.0, 68.9, 69.9, 70.0, 70.1, 70.2, 72.6, 122.8, 122.9, 137.0; MS (FAB) m/z 1007.53 (M-OMs)$^+$; HRMS (FAB TOF) m/z calcd for $C_{43}H_{83}O_{20}N_4S$ (M-OMs)$^+$ 1007.5321, found 1007.5320.

Typical Procedure of Nucleophilic Hydroxylation in Table 1 (Entry 4). K_2CO_3 (415 mg, 3 mmol) was added to the mixture of 2-(3-bromopropoxy)naphthalene (**4**, 264 mg, 1.0 mmol) and hexaEG-DHIM (1.11 g, 1.0 mmol) in water (4 mL). The reaction mixture was stirred over 5 h at 110 °C. The reaction time was determined by checking TLC. The reaction mixture was filtered and washed with diethyl ether, and the filtrate was evaporated under reduced pressure. Flash column chromatography (10% EtOAc/hexanes) of the filtrate afforded 192 mg (0.95 mmol, 95%) of 2-(3-hydroxypropoxy)-naphthalene (**5a**) as a white solid; mp: 103−105 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.86 (bs, 1H), 2.06−2.12 (m, 2H), 3.89 (t, J = 5.5 Hz, 2H), 4.22 (t, J = 6.2 Hz, 2H), 7.12−7.14 (m, 2H), 7.32 (t, J = 6.8 Hz, 1H) 7.42 (t, J = 6.9 Hz, 1H), 7.70−7.76 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.1, 60.6, 65.8, 106.8, 118.9, 123.8, 126.5, 126.9, 127.7, 129.1, 129.5, 134.6, 156.8. Registry No. provided by the author: 7598−29−0.

Procedure of Entry 1 in Table 1. Prepared according to the typical procedure of hydroxylation (entry 4 in Table 1) except using the mixture solution of 1,4-dioxane (2 mL) and water (2 mL) for 9 h instead of using water (4 mL). This reaction provided 193 mg of **5a** in 95% yield.

Procedure of Entry 2 in Table 1. Prepared according to the typical procedure of hydroxylation except using $NaHCO_3$ (252 mg, 3 mmol) in the mixture solution of 1,4-dioxane (2 mL) and water (2 mL) instead of using K_2CO_3 (415 mg, 3 mmol) in water (4 mL). This reaction provided 190 mg of **5a** in 94% yield.

Procedure of Entry 3 in Table 1. Prepared according to the typical procedure of hydroxylation except using $NaHCO_3$ (252 mg, 3 mmol) for 24 h instead of using K_2CO_3 (415 mg, 3 mmol). This reaction provided 178 mg of **5a** in 88% yield.

Procedure of Entry 5 in Table 1. Prepared according to the typical procedure of hydroxylation except no use of hexaEG-DHIM (1.11 g, 1.0 mmol). This reaction provided only 39 mg of **5a** in 19% yield.

Procedure of Entry 6 in Table 1. Prepared according to the typical procedure of hydroxylation except using [dihexaEGim][OMs] (692 mg, 1.0 mmol) instead of using hexaEG-DHIM (1.11 g, 1.0 mmol). This reaction provided 192 mg of **5a** in 95% yield after 12 h.

Procedure of Entry 7 in Table 1. Prepared according to the typical procedure of hydroxylation (entry 4) except using [hexaEGmim][OMs] (443 mg, 1.0 mmol) instead of using hexaEG-DHIM (1.11 g, 1.0 mmol). This reaction provided 191 mg of **5a** in 94% yield after 16 h.

Procedure of Entry 8 in Table 1. Prepared according to the typical procedure of hydroxylation (entry 4) except using [bmim]-[OMs] (235 mg, 1.0 mmol) instead of using hexaEG-DHIM (1.11 g, 1.0 mmol). This reaction provided 187 mg of **5a** in 92% yield after 48 h.

Procedure of Entry 9 in Table 1. Prepared according to the typical procedure of hydroxylation (entry 4) except using TBAOH·$30H_2O$ (2.40 g, 3.0 mmol) instead of using hexaEG-DHIM (1.11 g, 1.0 mmol) and K_2CO_3 (415 mg, 3.0 mmol). This reaction provided 61 mg of **5a** in 30% yield after 5 h.

Procedure of Entry 10 in Table 1. Prepared according to the typical procedure of hydroxylation (entry 4) except using 18-crown-6 (264 mg, 1.0 mmol) and KOH (169 mg, 3 mmol) instead of using [hexaEG(hexaEGim)$_2$][OMs]$_2$ and K_2CO_3 (415 mg, 3 mmol). This reaction provided 46 mg of **5a** in 23% yield after 5 h.

1,3-Propanediol (Entry 1 in Table 2). Prepared according to the typical procedure (entry 4 in Table 1) of hydroxylation except using 3-bromo-1-propanol (139 mg, 1.0 mmol) for 1 h instead of using 2-(3-bromopropoxy)naphthalene (**4**). This reaction provided 73 mg (0.96 mmol) of 1,3-propanediol in 96% yield as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80−186 (m, 2H), 1.96 (bs, 2H), 3.83−3.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3, 59.6; MS (EI) m/z 77 (M^+ + H); HRMS (FAB TOF) m/z calcd for $C_3H_9O_2$ (M^+ + H) 77.0603, found 77.06012. Registry No. provided by the author: 504−63−2.

Hexaethylene Glycol (Entry 2 in Table 2). Prepared according to the typical procedure of hydroxylation except using 17-bromo-3,6,9,12,15-pentaoxaheptadecan-1-ol (344 mg, 1.0 mmol) for 1 h instead of using **4**. This reaction provided 277 mg (0.98 mmol) of hexaethylene glycol in 98% yield as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (t, J = 7.2 Hz, 4H), 3.52−3.6 (m, 16H), 3.66 (t, J = 7.2 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 61.6, 70.3, 70.5, 70.6, 72.7; MS (EI) m/z 283 (M^+ + H); HRMS (FAB TOF) m/z calcd for $C_{12}H_{27}O_7$ (M^+ + H) 283.1757, found 283.1755. Registry No. provided by the author: 2615−15−8.

1-(3-Hydroxypropyl)-4-nitroimidazole (Entry 3 in Table 2). Prepared according to the typical procedure of hydroxylation except using 1-(3-bromopropyl)-4-nitroimidazole (233 mg, 1.0 mmol) for 1 h instead of using **4**. This reaction provided 163 mg (0.95 mmol) of 1-(3-hydroxypropyl)-4-nitroimidazole in 95% yield as a white solid; mp: 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02−2.05 (m, 2H), 3.66 (t, J = 8.5 Hz, 2H), 4.19 (t, J = 7.0 Hz, 2H), 7.45 (s, H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 34.2, 46.4, 59.1, 121.9, 138.6, 148.5; MS (EI) m/z 171 (M^+); HRMS (EI TOF) m/z calcd for $C_6H_9N_3O_3$ (M^+) 171.0644, found 171.0642. Registry No. provided by the author: 13230−17−6.

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1-(2-Hydroxyethyl)naphthalene (Entry 4 in Table 2). Prepared according to the typical procedure of hydroxylation except using 1-(2-bromoethyl)naphthalene (234 mg, 1.0 mmol) for 12 h instead of using **4**. This reaction provided 164 mg (0.95 mmol) of 1-(2-hydroxyethyl)-naphthalene in 95% yield as a white solid; mp: 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (bs, 1H), 3.33 (t, J = 6.4 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 7.35−7.49 (m, 4H), 7.75 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0, 62.8, 123.5, 125.4, 125.5, 125.9, 127.0, 127.1, 128.7, 132.0, 133.8, 134.4; MS (EI) m/z 172 (M^+); HRMS (FAB TOF) m/z calcd for $C_{12}H_{12}O$ (M^+) 172.0888, found 172.0888. Registry No. provided by the author: 773−99−9.

2-(2-Hydroxypropoxy)naphthalene (Entry 5 in Table 2). Prepared according to the typical procedure of hydroxylation except using 2-(2-bromopropoxy)naphthalene (264 mg, 1.0 mmol) for 6 h instead of using **4**. This reaction provided 176 mg (0.87 mmol) of 2-(2-hydroxypropoxy)naphthalene in 87% yield as a white solid; mp: 82−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 7.6 Hz, 3H), 2.38 (s, 1H), 3.92 (t, J = 18 Hz, 1H), 4.06 (d, J = 12 Hz, 1H), 4.27−4.27 (m, 1H), 7.14−7.25 (m, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.71−7.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 64.5, 73.5, 107.1, 118.9, 124.0, 126.7, 127.0, 127.9, 129.3, 129.7, 134.7, 156.7; MS (EI) m/z 202 (M^+); HRMS (EI TOF) m/z calcd for $C_{13}H_{14}O_2$ (M^+) 202.0993, found 202.0993. Registry No. provided by the author: 108298−91−5.

2-(Hydroxymethyl)naphthalene (Entry 6 in Table 2). Prepared according to the typical procedure of hydroxylation except using 2-(bromomethyl)naphthalene (220 mg, 1.0 mmol) for 1 h instead of using **4**. This reaction provided 153 mg (0.97 mmol) of 2-(hydroxymethyl)naphthalene in 97% yield as a white solid; mp: 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (bs, 1H), 4.84 (s, 2H), 7.45−7.49 (m, 3H), 7.78−7.83 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 65.4, 125.5, 125.7, 126.1, 126.4, 128.0, 128.2, 128.5, 133.2, 133.6, 138.6; MS (EI) m/z 158 (M^+); HRMS (EI TOF) m/z calcd for $C_{11}H_{10}O$ (M^+) 158.0732, found 158.0730. Registry No. provided by the author: 1592−38−7.

α-Hydroxy-3-picoline-*N*-oxide (Entry 9 in Table 2). Prepared according to the typical procedure of hydroxylation except using 3-chloro-picoline *N*-oxide (143 mg, 1.0 mmol) for 3 h instead of using **4**. This reaction provided 120 mg (0.96 mmol) of α-hydroxy-3-picoline-*N*-oxide in 96% yield as a white solid; mp: 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 2H), 5.23 (bs, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.23−7.27 (m, 1H), 7.95 (d, J = 6.0 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.6, 125.5, 125.9, 137.0, 137.2, 142.1; MS (EI) m/z 126 (M^+ + H); HRMS (FAB TOF) m/z calcd for $C_6H_8NO_2$ (M^+ + H) 126.0555, found 126.0554. Registry No. provided by the author: 6968−72−5.

3-*O*-(3-Hydroxypropyl)estrone (Entry 10 in Table 2). Prepared according to the typical procedure of hydroxylation except using 3-*O*-(3-bromopropyl)estrone (390 mg, 1.0 mmol) for 5 h instead of using **4**. This reaction provided 318 mg (0.97 mmol) of 3-*O*-(3-hydroxypropyl)estrone in 97% yield as a white solid; mp: 80−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.35−1.71 (m, 7H), 1.89−2.16 (m, 5H), 2.27 (s, 1H), 2.37 (s, 1H), 2.41 (q, J = 6.4 Hz, 2H), 2.80−2.94 (m, 2H), 3.82 (t, J = 6.4 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 6.63 (s, 1H), 6.66 (d, J = 2.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 25.9, 26.5, 29.6, 31.5, 32.0, 35.8, 38.3, 43.9, 48.0, 50.4, 60.6, 65.8, 112.0, 114.5, 126.3, 132.2, 137.8, 156.7; MS (EI) m/z 228 (M^+); HRMS (EI) m/z calcd for $C_{21}H_{28}O_3$ (M^+) 328.2038, found 328.2037. Registry No. provided by the author: 83876−72−6.

***N*-Fmoc-2-hydroxymethylaniline (7, Scheme 2).** hexaEG-DHIM (1.11 g, 1.0 mmol) was added to the mixture of *N*-Fmoc-2-chloromethylaniline (**6**, 363 mg, 1.0 mmol) in water (4 mL). The reaction mixture was stirred over 3 h at 110 °C. The reaction time was determined by checking TLC. The reaction mixture was extracted with diethyl ether (3 × 10 mL), dried on sodium sulfate, and concentrated under reduced pressure on rotary evaporator. Flash column chromatography (15% EtOAc/hexanes) of the residue afforded 310 mg (0.90 mmol, 90%) of *N*-Fmoc-2-hydroxymethylaniline (**7**) as a white solid. The reused hexaEG-DHIM in water were used directly for new cycle. This cycle proceeded ten times; mp: 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (bs, 1H), 4.29 (t, J = 7.0 Hz, 1H), 3.96 (t, J = 7.2 Hz, 2H), 4.58 (s, 2H), 7.05−7.079 (m, 1H), 7.23−7.53 (m, 7H), 7.85 (d, J = 7.2 Hz, 2H), 7.76 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.1, 64.4, 67.2, 120.0, 123.6, 125.1, 127.1, 127.8, 128.8, 129.3, 137.5, 141.3, 143.7, 143.8, 153.9; MS (EI) m/z 345 (M^+); HRMS (EI TOF) m/z calcd for $C_{22}H_{19}NO_3$ (M^+) 345.1365, found 345.1365.

Analytical Data of Substrates. *2-(3-Bromopropoxy)-naphthalene (**4**, Table 1).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36−2.43 (m, 2H), 3.67 (t, J = 6.6 Hz, 2H), 4.23 (t, J = 5.6 Hz, 2H), 7.14−7.17 (m, 2H), 7.34−7.49 (m, 2H), 7.74−7.80(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 32.2, 65.2, 106.6, 118.8, 123.7, 126.4, 126.7, 127.6, 128.9, 129.4, 134.4, 156.5. Registry No. provided by the author: 3245−62−3.

*N-Fmoc-2-chloromethylaniline (**6**, Scheme 2).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (t, J = 7.0 Hz, 1H), 4.54 (d, J = 7.2 Hz, 2H), 4.62 (s, 2H), 6.99 (br, 1H), 7.12−7.16 (m, 1H), 7.31−7.45 (m, 6H), 7.62−7.80 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 47.1, 67.3, 120.0, 124.8, 125.0, 127.1, 127.8, 130.0, 130.1, 136.4, 141.3, 143.7, 153.8; MS (EI) 363 (M^+), 178 (100), 165, 132; HRMS (EI) calcd for $C_{22}H_{18}ClNO_2$ (M^+), 363.1026, found 363.1032.

1-(3-Bromopropyl)-4-nitroimidazole (Entry 3 in Table 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35−2.40 (m, 2H), 3.37 (t, J = 6.2 Hz, 2H), 4.28 (t, J = 6.2 Hz, 2H), 7.51 (s, 2H), 7.82 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.7, 32.8, 46.1, 119.2, 136.3, 148.4. Registry No. provided by author: 126401−78−3.

1-(2-Bromoethyl)naphthalene (Entry 4 in Table 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63−3.72 (m, 4H), 7.37−7.58 (m, 4H), 7.80 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 37.0, 123.3, 125.7, 126.0, 126.6, 127.2, 128.0, 129.2, 131.7, 134.2, 135.1. Registry No. provided by the author: 13686−49−2.

2-(2-Bromopropoxy)naphthalene (Entry 5 in Table 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.78 (d, J = 6.2 Hz, 3H), 4.09−4.13 (m, 1H), 4.27−4.36 (m, 2H), 7.06 (d, J = 2.8 Hz, 1H), 7.09 (dd, J = 11.7, 2.8 Hz, 1H), 7.28 (t, J = 15.1 Hz, 1H), 7.38 (t, J = 15.1 Hz, 1H), 7.63−7.72 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.9, 45.3, 71.2, 107.2, 118.8, 124.0, 126.6, 126.9, 127.8, 129.3, 129.7, 134.5, 156.2. Registry No. provided by the author: 601470−35−3.

2-(3-Chloropropoxy)naphthalene (Entry 7 in Table 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28−2.32 (m, 2H), 3.79 (t, J = 6.2 Hz, 2H), 4.23 (t, J = 6.2 Hz, 2H), 7.12−7.15 (m, 2H), 7.34 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 7.72−7.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 41.6, 64.2, 106.6, 118.8, 123.6, 126.4, 126.7, 127.6, 128.9, 129.4, 134.4, 156.6. Registry No. provided by the author: 56231−42−6.

2-(3-Iodopropoxy)naphthalene (Entry 8 in Table 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32−2.38 (m, 2H), 3.43 (t, J = 6.6 Hz, 2H), 4.16 (t, J = 5.8 Hz, 2H), 7.15−7.17 (m, 2H), 7.35−7.49 (m, 2H), 7.49−7.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.7, 32.8, 67.1, 106.6, 118.8, 123.6, 126.4, 126.7, 127.6, 128.1, 129.4, 134.4, 156.5. Registry No. provided by the author: 380363−99−5.

3-Chloro-picoline N-oxide (Entry 9 in Table 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (s, 2H), 7.27−7.32 (m, 2H), 8.17 (d, J = 6.0 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 41.7, 125.8, 126.1, 137.0, 138.9, 139.1; MS (EI) m/z 143 (M^+, 100); HRMS (EI TOF) calcd for C_6H_6ClNO: (M^+) 143.0138, found 143.0137.

3-O-(3-Bromopropyl)estrone (Entry 10 in Table 2). White solid: mp 137.8−138.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.39−1.69 (m, 7H), 1.92−2.19 (m, 3H), 2.26 (s, 1H), 2.29 (q, J = 6.4 Hz, 2H), 2.39 (br, 1H), 2.46−2.58 (m, 1H), 2.87−2.90 (m, 2H), 3.59 (t, J = 6.4 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 6.65 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 8.8, 2.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 25.9, 26.5, 29.6, 30.1, 31.5, 32.4, 35.8, 38.3, 43.9, 48.0, 50.4, 65.2, 112.1, 114.5, 126.3, 132.3, 137.8, 156.6, 220.8. Registry No. provided by the author: 975−65−5.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds and picture of hexaEG-DHIM. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00901.

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Notes

The authors declare no competing financial interest.

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