Amphiphilic Viologen: Electrochemical Generation of Organic Reductant and Pd-Catalyzed Reductive Coupling of Aryl Halides in Water

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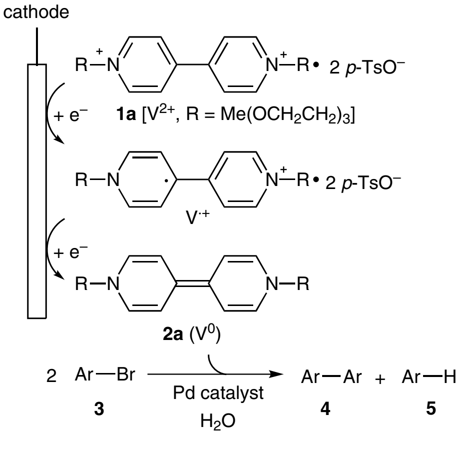
Abstract: Electroreduction of 1,1′-bis(methoxyethoxyethoxyethyl)-4,4′-bipyridinium tosylate generated amphiphilic organic reductants, which promoted the Pd-catalyzed reductive coupling of aryl bromides in water to give the corresponding biaryls. The yields and selectivity of biaryls depended on the length of ethyleneoxy groups and substituents of the aryl bromides.

Key words: electron transfer, palladium, reduction, coupling, arenes

Organic reactions in water are of current interest in organic synthesis.[1] Water is a cheap, nonflammable, and nontoxic solvent. In addition, the reactions are accelerated and unique selectivity is observed caused by hydrophobic effects. Water is also an ideal solvent for electroorganic synthesis[2,3] since dielectric constant of water is high enough to pass electricity efficiently in the presence of a small amount of supporting electrolytes.

Viologen derivatives (1,1′-dialkyl-4,4′-bipyridinium salt, V^{2+}) are easily prepared by N-alkylation of 4,4′-bipyridyl and are stable in the air. Reduction of V^{2+} gives the corresponding radical cation $V^{\bullet+}$ and quinoid V^0 (Scheme 1), both of them work as organic reductants.[4]



Scheme 1 Electrochemical preparation and Pd-catalyzed reductive coupling of aryl bromides

The viologen V^{2+}/quinoid V^0 redox pair is usually used in organic–aqueous mixed solvent since V^{2+} dissolves in water, whereas the corresponding V^0 is insoluble in water.[5,6] We found that amphiphilic viologens V^{2+}/quinoids V^0 having poly(ethylene glycol) (PEG) groups dissolve in water, and the quinoids V^0 work as reductants in an aqueous medium. In this paper, we describe that reductive coupling of aryl bromides proceeds in water by using the PEG-modified amphiphilic viologen **1a**.

PEG-modified amphiphilic viologen, 1,1′-bis(methoxyethoxyethoxyethyl)-4,4′-bipyridinium tosylate (**1a**), was prepared by treatment of 4,4′-bipyridyl with two molar amount of $Me(OCH_2CH_2)_3OTs$ at 120 °C in 96% yield as a brown viscous oil.[7] In a similar manner, viologen **1b**–**e** [**1b**: R = $MeOCH_2CH_2$, **1c**: R = $Me(OCH_2CH_2)_2$, **1d**: R = Me, **1e**: R = Bu] were prepared by treatment of 4,4′-bipyridyl with $MeOCH_2CH_2OTs$, $Me(OCH_2CH_2)_2OTs$, MeOTs, and BuOTs, respectively.[8] Viologen **1a** was soluble in water and MeOH, whereas **1a** was insoluble in usual organic solvents such as hexane, Et_2O, toluene, and EtOAc. A cyclic voltammogram of **1a** in an aqueous Et_4NOTs (0.2 M) solution (vs. Ag/AgCl) exhibited two sets of reversible redox peaks at –0.57 V (**1a**/$V^{\bullet+}$) and –1.00 V ($V^{\bullet+}$/**2a**; Figure 1). Yields and redox potential values of **1b**–**e** are summarized in Table 1.

Table 1 Yields and Redox Potential Values of Compounds **1a**–**e**

Entry	Viologen	R	Yield (%)[a]	$E_{1/2}$[b]/V	
				1/$V^{\bullet+}$	$V^{\bullet+}$/**2**
1	**1a**	$Me(OCH_2CH_2)_3$	96	–0.57	–1.00
2	**1b**	$MeOCH_2CH_2$	87	–0.55[c]	–0.93[c]
3	**1c**	$Me(OCH_2CH_2)_2$	62	–0.57	–1.01
4	**1d**	Me	82	–0.58[c]	–0.96[c]
5	**1e**	Bu	86	–0.52[c]	–0.92[c]

[a] Isolated yield.

[b] Viologen (10 mM), Et_4NOTs (0.2 M), H_2O, (GC)–(Pt)–(Ag/AgCl), scan rate: 100 mV/s; reversible peaks. $E_{1/2} = (E_{pa} + E_{pc})/2$; E_{pa} = anodic peak potential value; E_{pc} = cathodic peak potential value.

[c] In MeCN–H_2O (3:1).

A typical procedure of electroreduction of **1a** to **2a** and subsequent reductive coupling of aryl bromide **3a** in water is as follows. The electroreduction was carried out in a divided cell equipped with an Mg rod anode (ø 0.6 cm) and a Pt plate cathode (1.0 × 1.5 cm²). In the cathodic chamber

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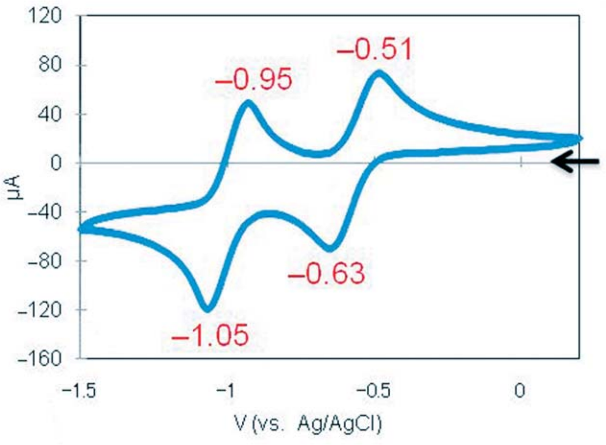


Figure 1 Cyclic voltammogram of **1a**. *Reagents and conditions*: **1a** (10 mM), aq Et_4NOTs (0.2 M, 10 mL); working electrode: GC, counter electrode: Pt, reference electrode: Ag/AgCl, scan rate: 100 mV/s.

was placed an aqueous $NaClO_4$ (0.2 M, 4 mL) solution of **1a** (0.5 mmol), and in the anodic chamber was placed an aqueous $NaClO_4$ (0.2 M, 4 mL) solution. Electroreduction of **1a** was carried out at room temperature under constant current conditions (30 mA) until 2 F/mol **1a** of electricity was passed to afford a dark purple solution of **2a**. To a mixture of **3a** (0.25 mmol) and a catalytic amount of $Pd(OAc)_2$ (5 mol%) was added the catholyte by cannulation, and the whole mixture was stirred at 60 °C for four hours under argon atmosphere. After usual workup, the desired coupling product, 4,4′-dipropanoylbiphenyl (**4a**) and reduced byproduct propiophenone (**5a**) were obtained in 90% and 8% yield, respectively (Table 2, entry 1).

The PEG group of **1a** played an important role:[9] Quinoids **2** derived from methyl viologen **1d** and butyl viologen **1e** gave **4a**/**5a** in 17% and 25% and 31% and 6% yields, respectively, and half of the starting material **3a** was recovered unchanged (Table 2, entries 4 and 5). The length of the PEG groups [n of $Me(OCH_2CH_2)_n$] also affected on the yields of **4a**. Viologen having methoxyethyl group (**1b**, n = 1) gave a similar result (**4a**/**5a**/**3a** = 30%, 12%, and 45%, Table 2, entry 2) with butyl viologen **1e**. Though homocoupling of **3a** with methoxyethoxyethylated viologen **1c** (n = 2) gave **4a** as a major product (**4a**/**5a**/**3a** = 59%, 8%, and 19%, Table 2, entry 3), **1c** was less effective than **1a**. The ethyleneoxy group in viologen would increase the solubility of the reduced form **2** in water. In addition, the substrate **3a** and Pd catalyst would interact with the ethyleneoxy group of **2a** to make an aggregate (Figure 2), and therefore, electron transfer and oxidative addition would proceed smoothly.

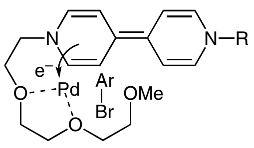


Figure 2 A plausible aggregate of amphiphilic quinoid **2a**, Pd catalyst, and substrate ArBr

Table 2 Effects of Viologen on the Reductive Coupling of 4-Bromopropiophenone (**3a**)

Entry	Viologen	R	Yield of **4a** (%)[a]	Yield of **5a** (%)[b]	Yield of **3a** (%)[b]
1	**1a**	$Me(OCH_2CH_2)_3$	90	8	0
2	**1b**	$MeOCH_2CH_2$	30	12	45
3	**1c**	$Me(OCH_2CH_2)_2$	59	8	19
4	**1d**	Me	17	25	53
5	**1e**	Bu	31	6	49

[a] Isolated yield.
[b] Determined by ^1H NMR.

Among thus far examined catalysts, $Pd(OAc)_2$ gave the best result (Table 3, entry 1). $PdCl_2$ and $Pd_2(dba)_3$ gave **4a**/**5a**/**3a** in 26%, 18%, and 53% yields and 62%, 9%, and 23% yields, respectively (Table 3, entries 2 and 3). Pd/C (10% Pd/C) gave the reduced product **5a** as a major product (26% yield, Table 3, entry 4). Palladium catalyst was indispensable: the reductive coupling reaction did not occur in the presence of Ni catalysts in place of Pd catalysts (Table 3, entries 5 and 6) and in the absence of catalysts (Table 3, entry 7).

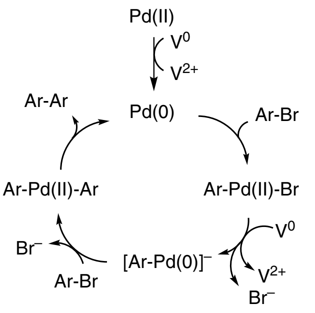
Table 3 Effects of Catalyst

Entry	Catalyst	Yield of **4a** (%)[a]	Yield of **5a** (%)[b]	Yield of **3a** (%)[b]
1	$Pd(OAc)_2$	90	8	0
2	$PdCl_2$	26	18	53
3	$Pd_2(dba)_3$	62	9	23
4	10% Pd/C	9	26	56
5	$Ni(OAc)_2{\cdot}4H_2O$	n.d.[c]	n.d.[c]	
6	$NiBr_2(bpy)$	n.d.[c]	n.d.[c]	
7	none	n.d.[c]	n.d.[c]	

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Not detected.

The reductive coupling was carried out with several aryl halides (Table 4).

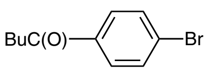
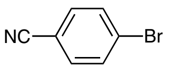
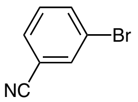
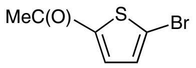
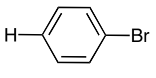
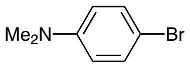
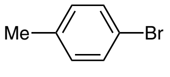
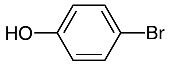
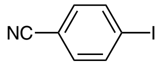
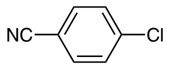
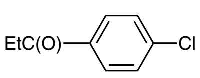
The coupling of aryl bromides having electron-withdrawing groups such as keto (**3b**) and cyano (**3c**,**d**) groups proceeded smoothly to give the corresponding biaryls **4b**, **4c**, and **4d** in good yields (Table 4, entries 1–3). Heteroaromatic compound, 2-acetyl-5-bromothiophene (**3e**), gave dithiophene **4e** in 82% yield (Table 4, entry 4). Unsubstituted bromobenzene (**3f**) gave biphenyl **4f** in 75% yield (Table 4, entry 5). On the other hand, aryl bromides having electron-donating groups such as dimethylamino (**3g**), methyl (**3h**), and hydroxyl (**3i**) groups gave the corre-



Scheme 2 A plausible mechanism

sponding biaryls **4g**, **4h**, and **4i** in moderate yields (Table 4, entries 6–8). 4-Iodobenzonitrile (**3j**) and 4-choropropiophenone (**3l**) gave the corresponding biaryls in low yields, and homocoupling of 4-chlorobenzonitrile (**3k**) did not proceed at all (Table 4, entries 9–11).

Table 4 Reductive Coupling of Several Aryl Halides

Entry	ArX		Temp (°C)	Time (h)	Yield of **4** (%)[a]
1		**3b**	60	6	66
2		**3c**	100	4	74
3		**3d**	60	24	92
4		**3e**	100	4	82
5		**3f**	60	24	75
6		**3g**	80	24	45
7		**3h**	60	24	25
8		**3i**	60	22	34
9		**3j**	100	4	29
10		**3k**	100	24	0
11		**3l**	60	24	31

[a] Isolated yield of biaryl **4**.

A plausible mechanism of the reductive coupling is as follows (Scheme 2). Pd(II) species would be reduced with V^0 to give Pd(0) active species. Oxidative addition of ArBr **3** on the Pd(0) would give ArPd(II)Br. Reduction of ArPd(II)Br with V^0 would afford [ArPd(0)]$^-$. The subsequent reaction of [ArPd(0)]$^-$ with additional ArBr would produce ArPd(II)Ar. Reductive coupling from ArPd(II)Ar would give Ar–Ar **4** and Pd(0) species. Dissociation of [ArPd(0)]$^-$ to Ar$^-$ and Pd(0) followed by protonation would give ArH **5**.

Substituents on the ArBr affect the reduction of ArPd(II)Br to [ArPd(0)]$^-$: Electron-withdrawing substituents would decrease the electron density of Pd in ArPd(II)Br to accelerate the reduction giving [ArPd(0)]$^-$, whereas electron-donating substituents would increase the electron density to prevent the reduction. In the case of ArCl, oxidative addition of ArCl on the Pd(0) and/or [ArPd(0)]$^-$ would not occur efficiently.

In conclusion, amphiphilic organic reductant V^0, electrochemically generated from 1,1′-bis(methoxyethoxyethoxyethyl)-4,4′-bipyridinium (V^{2+}) tosylate (**1a**), promoted the Pd-catalyzed reductive coupling of aryl bromides in water to give the corresponding biaryls. The yields and selectivity of biaryls were affected by the length of ethyleneoxy groups and substituents of the aryl bromides.[10]

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(5) Octyl viologen bis(triflimide) and the corresponding quinoid dissolve in organic solvent to promote the reductive homocoupling of aryl halide. See: Kuroboshi, M.; Kobayashi, R.; Nakagawa, T.; Tanaka, H. *Synlett* **2009**, 85.

(6) Viologen also promotes the reductive homocoupling of aryl halides in ionic liquid. See: Kuroboshi, M.; Kuwano, A.; Tanaka, H. *Electrochemistry* **2008**, 862.

(7) **Preparation of 1a**

In a round-bottomed flask were placed 4,4′-bipyridyl (3.531 g, 23 mmol) and 3,6,9-trioxadecyl *p*-tosylate (14.39 g, 45 mmol). The mixture was stirred at 120 °C for 24 h under argon atmosphere to form a viscous layer. The supernatant was decanted off, and the viscous layer was washed with Et_2O and toluene (2 × 10 mL), successively. The viscous liquid layer was concentrated under reduced pressure to give 1,1′-bis(3,6,9-trioxadecyl)-4,4′-bipyridinium bis(*p*-toluenesulfonate) (**1a**, 17.14 g, 22 mmol, 96%) as a brown liquid. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.28$ (s, 6 H), 3.28 (s, 6 H), 3.42–3.53 (m, 16 H), 3.85 (br, 4 H), 4.93 (br, 4 H), 7.11 (d, $J = 8.1$ Hz, 4 H), 7.69 (d, $J = 8.1$ Hz, 4 H), 8.71 (d, $J = 6.8$ Hz, 4 H), 9.24 (d, $J = 6.8$ Hz, 4 H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 21.04$, 58.69, 61.18, 68.89, 69.91, 70.08, 70.14, 71.56, 125.66, 126.64, 128.71, 1139.42, 143.25, 146.60, 148.87; IR (neat): 3464, 3127, 3059, 2921, 2876, 1638, 1451, 1191, 1122, 822 cm^{-1}.

(8) **1,1′-Bis(2-methoxyethyl)-4,4′-bipyridinium Bis(*p*-toluenesulfonate) (1b)**

Colorless solids. ^{1}H NMR (200 MHz, D_2O): $\delta = 2.13$ (s, 6 H), 3.19 (s, 6 H), 3.79 (t, $J = 5.0$ Hz, 4 H), 4.68 (t, $J = 5.0$ Hz, 4 H), 7.08 (d, $J = 8.3$ Hz, 4 H), 7.40 (d, $J = 8.3$ Hz, 4 H), 8.26 (d, $J = 7.0$ Hz, 4 H), 8.85 (d, $J = 7.0$ Hz, 4 H). ^{13}C NMR (50 MHz, CD_3OD): $\delta = 21.3$, 59.2, 62.7, 71.3, 126.8, 127.8, 129.8, 141.6, 143.5, 147.5, 151.3. IR (KBr): 3532, 3451, 3134, 3062, 2992, 2864, 1639, 1510, 1448, 1191, 1120, 1035, 568 cm^{-1}.

1,1′-Bis(3,6-dioxaheptyl)-4,4′-bipyridinium Bis(*p*-toluenesulfonate) (1c)

Colorless solids. ^{1}H NMR (200 MHz, D_2O): $\delta = 2.15$ (s, 6 H), 3.09 (s, 6 H), 3.32–3.36 (m, 4 H), 3.44–3.49 (m, 4 H), 3.86 (t, $J = 4.4$ Hz, 4 H), 4.63–4.76 (m, 4 H), 7.11 (d, $J = 7.7$ Hz, 4 H), 7.42 (d, $J = 7.7$ Hz, 4 H), 8.30 (d, $J = 6.2$ Hz, 4 H), 8.89 (d, $J = 6.2$ Hz, 4 H). ^{13}C NMR (150 MHz, CD_3OD): $\delta =$ 21.3, 59.1, 62.7, 70.0, 71.2, 72.7, 126.9, 127.7, 129.9, 141.6, 143.7, 147.6, 151.2. IR (KBr): 3509, 3131, 3055, 2879, 1640, 1442, 1192, 1123, 1033, 685 cm^{-1}.

1,1′-Dimethyl-4,4′-bipyridinium Bis(*p*-toluenesulfonate) (1d)

Yellow solids. ^{1}H NMR (200 MHz, D_2O): $\delta = 2.18$ (s, 6 H), 4.31 (s, 6 H), 7.13 (d, $J = 8.2$ Hz, 4 H), 7.45 (d, $J = 8.2$ Hz, 4 H), 8.25 (d, $J = 6.9$ Hz, 4 H), 8.81 (d, $J = 6.9$ Hz, 4 H). ^{13}C NMR (150 MHz, CD_3OD): $\delta = 21.3$, 49.0, 126.8, 127.6, 130.0, 141.6, 143.7, 147.8, 150.4. IR (KBr): 3444, 3053, 3020, 2994, 1642, 1509, 1440, 1358, 1208, 1119, 818, 683 cm^{-1}.

1,1′-Dibutyl-4,4′-bipyridinium Bis(*p*-toluenesulfonate) (1e)

Colorless solids. ^{1}H NMR (200 MHz, D_2O): $\delta = 0.71$ (t, $J =$ 7.4 Hz, 6 H), 1.13 (sext, $J = 7.4$ Hz, 4 H), 1.76 (quin, $J = 7.4$ Hz, 4 H), 2.07 (s, 6 H), 4.40 (t, $J = 7.4$ Hz, 4 H), 7.01 (d, $J =$ 8.1 Hz, 4 H), 7.32 (d, $J = 8.1$ Hz, 4 H), 8.16 (d, $J = 6.7$ Hz, 4 H), 8.77 (d, $J = 6.7$ Hz, 4 H). ^{13}C NMR (150 MHz, CD_3OD): $\delta = 13.8$, 20.4, 21.3, 34.3, 62.9, 126.9, 128.2, 129.9, 141.6, 143.7, 147.0, 151.0. IR (KBr): 3434, 3127, 3054, 2957, 2870, 1643, 1450, 1169, 1120, 1035, 818 cm^{-1}.

(9) Viologens V^{2+} were easily soluble in H_2O, whereas the reduced form V^0 were soluble in organic solvents. Therefore, viologens were used in a mixed solution of H_2O–MeOH or H_2O–MeCN. The amphiphilic PEG group would increase the solubility of V^{2+}/V^0 as well as the substrates.

(10) Recycle use of aqueous viologen/Pd solution was also examined. In the second run, the recovered aqueous solution was placed in the cathodic chamber. The electroreduction was carried out under constant current conditions to generate V^0. Though the reaction conditions have not been optimized yet, **4a** was obtained in 40% yield.