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Reductive Coupling of Aromatic Aldehydes Promoted by an Aqueous $TiCl_3$/*t*BuOOH System in Alcoholic Cosolvents

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The *tert*-butoxyl radical, generated by the aqueous Ti^{III}/TBHP system, abstracts an H atom from alcoholic cosolvents (EtOH, *i*PrOH), leading to α-hydroxyalkyl radicals that reduce aromatic aldehydes to the corresponding 1,2-diols. The reactivities observed are explained by resonance stabilization of the α-hydroxybenzyl radicals formed in the electron-transfer (ET) process. Good Hammett-type correlations are obtained.

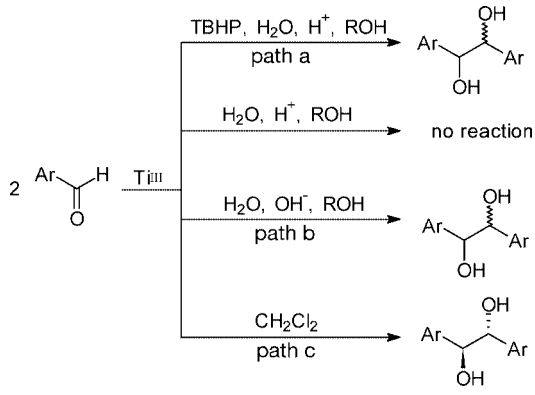
Introduction

The reactivity of the *tert*-butoxyl radical as a prototypical model for reactive oxygen-centered radicals has motivated numerous studies in organic, biological, and atmospheric chemistry,[1] and a large number of absolute rate constants for H atom abstraction reactions from a variety of substrates (ethers,[2] alcohols,[3] amines,[1,4] and hydrocarbons[1,5]) has been measured.[6]

We recently reported[7] that the *tert*-butoxyl radical, generated by aqueous Ti^{III} one-electron reduction of *tert*-butylhydroperoxide (TBHP), selectively abstracted an α-H atom from ethers affording α-ether radicals, which underwent chemoselective addition to an equilibrium mixture of an aldehyde and an amine leading to imine addition products in good yields without byproducts derived from the aldehyde.

While further investigating these reactions, we unexpectedly found that the Ti^{III}/TBHP redox system, when used in combination with an alcoholic cosolvent (EtOH, *i*PrOH), brings about the hydrodimerization of aromatic aldehydes in fair-to-high yields, depending on both the polar nature and the position of the X-substituent in the aromatic ring and the type of alcoholic cosolvent (Scheme 1, path a).

Earlier investigations by our laboratory showed that an aqueous $TiCl_3$ solution promoted pinacolization of aromatic aldehydes only in strong basic medium[8] (Scheme 1, path b) but not under acidic conditions, according to the fact that the reducing power of the aqueous Ti^{III} ion strongly increases with an increase in the pH of the solution.



Scheme 1. Effect of the reaction medium on the pinacolization of aromatic aldehydes.

We next[8e] found that by using a strictly anhydrous noncoordinating solvent (CH_2Cl_2), high *dl*-stereoselective pinacolization occurred (Scheme 1, path c) due to Ti^{III} carbonyl oxygen complexation, which lowers the reduction potential of the aldehyde.

Thus, on the basis of the above experimental findings, it seems a paradox that the addition of peroxide to an aqueous acidic Ti^{III} alcoholic solution could promote the reductive dimerization of aromatic aldehydes. Several EPR and laser flash photolysis studies showed that α-hydroxyalkyl radicals, mainly generated by hydroxy radical H atom abstraction from alcohols, bring about rapid one-electron reduction of substrates with high electron affinity (such as nitro compounds,[9] heteroaromatic bases, and quinones, etc.[10]). Then it should follow that, under our conditions, the Ti^{III}/TBHP system should initiate the generation of α-hydroxyalkyl radicals which, in turn, behave as the ac-

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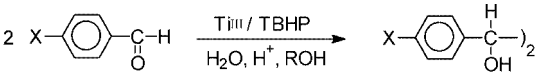
tual reductant of the aromatic aldehyde present, instead of the Ti^{III} ion.

The aim of the present report is to investigate the influence of the substituents at the aromatic ring in determining the substrate reactivity towards reduction by the Ti^{III}/TBHP aqueous acidic system in different alcoholic cosolvents.

Results and Discussion

After a survey to optimize the reaction conditions we found that upon dropwise addition of TBHP (5 mmol in 5 mL of EtOH or *i*PrOH) to a homogeneous solution of 4-CN-benzaldehyde (**1a**, 2 mmol) and $TiCl_3$ (15% aqueous acidic solution, 8 mmol) in either EtOH or *i*PrOH (10 mL), an exothermic reaction took place, leading to dimers **2a** (*meso*/*dl*, 1:1) in almost quantitative isolated yields (95%, Table 1) in ca. 5 min. Under the same experimental conditions, but in the absence of TBHP, **1a** was recovered unchanged, as already pointed out in Scheme 1.

Table 1. Reductive coupling of *para*-substituted benzaldehydes[a] by using an excess of TBHP.



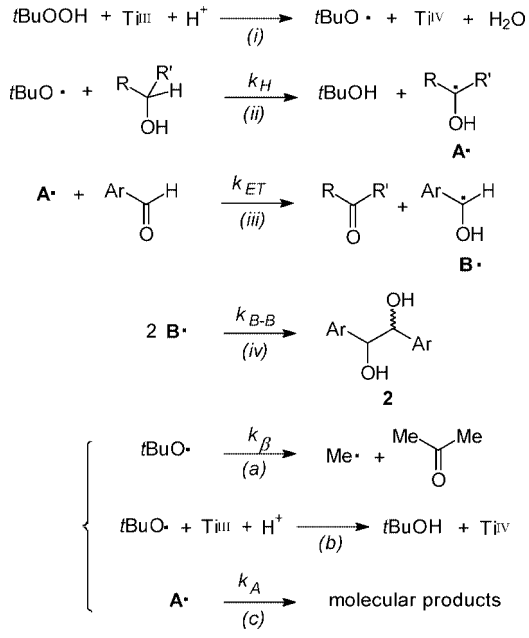
	1a-f	2a-f	
X	**1**	Yields of **2a–f** [%][b,c]	
		EtOH	*i*PrOH
CN	**1a**	95	95
$COCH_3$	**1b**	85	86
CO_2CH_3	**1c**	80	82
Br	**1d**	68	68
H	**1e**	35	58
CH_3	**1f**	24	46

[a] Molar ratio 1:2.5 for **1**/TBHP. [b] Isolated yields based on the aldehyde. [c] Ratio *meso*/*dl*, 1:1, determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

The reaction proceeds like a titration and can be visually monitored because the end is clearly showed by the change in color of the solution from blue to yellow, which occurs by the time (5 min) TBHP is added. Pinacol coupling reactions by using the above 2.5:1 over-stoichiometric amount of TBHP/aldehyde in either EtOH or *i*PrOH cosolvents, are summarized in Table 1.

Several comments are worth noting: (1) aromatic aldehydes bearing *para* electron-withdrawing substituents (**1a**–**d**) afforded corresponding diols **2** in good isolated yields, and similar results were obtained in both solvents, (2) with the less activated benzaldehyde and *p*-tolualdehyde, the desired diols were obtained in modest yields and the decrease was more pronounced in EtOH than in *i*PrOH, (3) the reduction is highly chemoselective: many functional groups (CN, CO_2Me, Br) are compatible with the conditions used and even *p*-acetylbenzaldehyde (**1b**) is selectively reduced at the aldehyde functionality.

The formation of dimers **2**, as well as the reactivity observed, can be explained by the reactions sequences reported in Scheme 2, paths *i*–*iv* (R = R′ = Me; R = H, R′ = Me).



Scheme 2. Mechanistic rationale.

The *tert*-butoxyl radical arising from Ti^{III} one-electron reduction of TBHP (path *i*) generates α-hydroxyalkyl radical **A**· by selective α-H atom abstraction from the solvent alcohol (path *ii*) in a fast process (k_H are 1.1×10^6 and 1.8×10^6 $M^{-1} s^{-1}$ for EtOH and *i*PrOH, respectively),[3a] due to favorable enthalpy balance[11] and polar factors.[12]

As shown by their redox potentials,[13] α-hydroxyalkyl radicals have a strong nucleophilic character which determines their fast oxidation; thus, the electron-transfer step (path *iii*), leading to the oxidation product of the alcohol and to the radical anion of the aromatic aldehyde, in protonated form **B**· because of the acidic medium, followed by the coupling of **B**· itself is the more plausible pathway leading to dimers **2**. The stereorandom formation of *meso* and *dl* dimers suggests that **B**· is not coordinated to the metal ion at the time of coupling.[8d]

As shown in Table 1, by working with an excess of TBHP, the difference in reducing power of the ethyl alcohol radical and of the isopropyl alcohol radical emerged only with aldehydes deactivated towards reduction, whereas a leveling effect was observed in the reduction of **1a**–**d**. If the ET mechanism outlined in Scheme 2 is operative, the fraction of electron transfer (e.g. dimers yield) should depend not only on the oxidizing power of the substrate, but also on the reducing strength of the α-hydroxyalkyl radical involved.[13]

To highlight the different reactivities of the two solvent radicals towards the same aldehyde, they have to be generated in a concentration that is comparable with that of the electron acceptor molecule. We reasoned that starting with

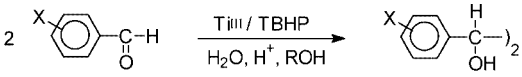
a stoichiometric 1:1 amount of TBHP/aldehyde the amount of **A**· would be equal to that of the *tert*-butoxyl radical not involved in the β-scission and in the reduction step [paths *a* and *b* of Scheme 2]. Then, the subsequent course of the reaction will only depend on the fate of **A**· so produced, which can either reduce the aldehyde (k_{ET}, path *iii*) or be consumed in competitive reactions leading to molecular products (k_A).[14]

For the reaction of *tert*-butoxyl radical (from Ti^{III}/TBHP at pH = 2) in the presence of *i*PrOH, Gilbert reported a value of 1:3.7 ± 0.4 for the ratio k_β:k_H.[15] Taking advantage of this value, determined under experimental conditions comparable to ours, we repeated the reduction of 4-CN-benzaldehyde in *i*PrOH by using a strictly controlled 1:1 stoichiometric amount of TBHP/aldehyde. The yield of **2a**, determined by ^{1}H NMR spectroscopy with an internal standard, was found to be 86% with respect to either the starting aldehyde or THBP.

According to Gilbert's value, this result could be interpreted to mean that only 14% of the initial TBHP is consumed in the competitive β-scission of the *tert*-butoxyl radical[16] (paths *i* and *a*), whereas the remaining 86% generates ketyl radical **A**· from *i*PrOH, (paths *i* and *ii*), which then quantitatively affords **B**· (path *iii*) by one-electron transfer to **1a**. Under these conditions, the lower reducing power of the ethyl alcohol radical showed itself, affording **2a** in 77% yield.

Thus, to have a more detailed picture concerning the structure–reactivity of both partners involved in these reactions, we performed the reduction of the aldehydes reported in Table 2 by using a 1:1 stoichiometric amount of TBHP/aldehyde. In Table 2 the aldehydes are listed in order of decreasing Hammett σ values of the substituents, and the yields of dimers **2** obtained in EtOH and *i*PrOH are reported in the fourth and fifth columns, respectively.

Table 2. Reductive coupling of *para*- and *meta*-substituted benzaldehydes by using a stoichiometric amount of TBHP/aldehyde.



1a-g **2a-g**

X	**1**	σ[a]	Yields of **2a**–**f** [%][b,c] EtOH	*i*PrOH
p-CN	**1a**	0.70	77	86
m-CN	**1a$_m$**	0.62	28	56
p-$COCH_3$	**1b**	0.47	60	75
p-CO_2CH_3	**1c**	0.44	55	73
m-$COCH_3$	**1b$_m$**	0.36	25	46
p-Br	**1d**	0.26	45	60
H	**1e**	0.00	25	43
p-CH_3	**1f**	–0.14	22	36
p-OCH_3	**1g**	–0.27	15	22

[a] Taken from ref.[17] [b] Yields, determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture with an internal standard, are based on starting **1**. [c] Ratio *meso*:*dl*, 1:1, by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Omitting the yields of dimers obtained in the reduction of *m*-CN and *m*-$COCH_3$ benzaldehydes (vide infra), very good linear correlations are observed between Hammett σ values of the substituents in the *para* position, and the yields of corresponding dimers **2** obtained in the two sets of reactions, as shown by the bold lines in Figures 1 (for EtOH) and 2 (for *i*PrOH).

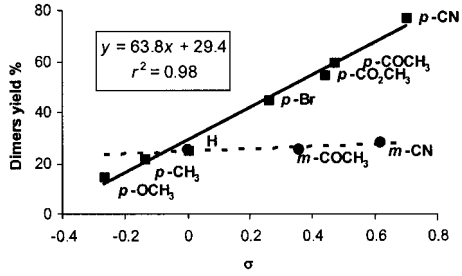


Figure 1. Plots of dimer yields vs. Hammett σ values of substituents for *para*- (■) and *meta*- (●) substituted benzaldehydes in EtOH cosolvent. The reported equation refers to the bold line.

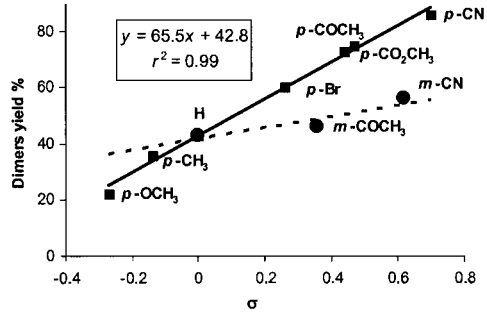


Figure 2. Plots of dimer yields vs. Hammett σ values of substituents for *para*- (■) and *meta*- (●) substituted benzaldehydes in *i*PrOH cosolvent. The reported equation refers to the bold line.

Since the two lines have almost the same slope (63.8 and 65.5, respectively), the difference in the axis intercepts (ca. 13% of dimers) can be taken as the average of the different reactivity of the two solvent radicals towards *para*-substituted benzaldehydes.

Unfortunately, the relative reactivities of substituted benzaldehydes cannot be experimentally determined under competitive conditions, since the formation of mixed diols introduces a notable source of errors. However, the fact that the two bold lines of Figures 1 and 2 are almost parallel allows to assume that, for a given alcohol radical, only the oxidizing power of the aldehyde determines k_{ET} (e.g. the dimer yields).

On the grounds of this assumption, the relative rates of the electron-transfer reactions to substituted benzaldehydes versus benzaldehyde **1e**, may be considered proportional to the relative yields of dimers **2x**/**2e** calculated from the data of Table 2.

In Figures 3 and 4 (reactions in EtOH and *i*PrOH, respectively), log(**2x**/**2e**) is plotted against Hammett's σ values of the same substituents X and, excluding the values of

meta-substituted- and of *para*-methoxybenzaldehyde, a very good linear correlation is observed for both the two sets of data.

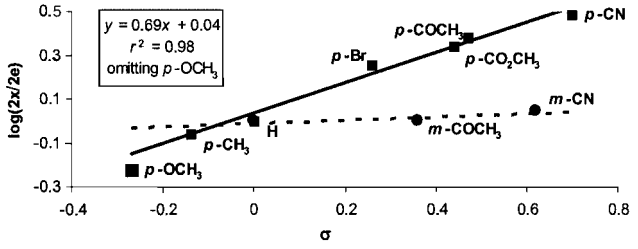


Figure 3. Plots of log(**2x/2e**) vs. Hammett σ values of substituents for *para*- (■) and *meta*- (●) substituted benzaldehydes in EtOH cosolvent. The reported equation refers to the bold line.

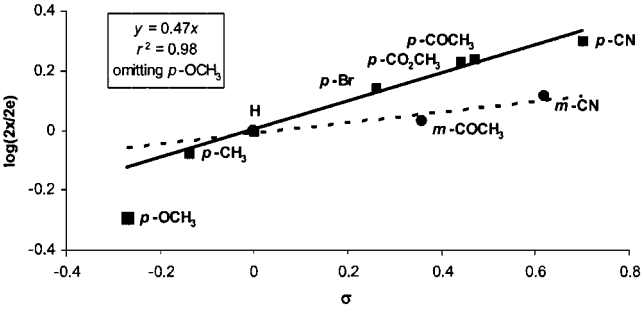


Figure 4. Plots of log(**2x/2e**) vs. Hammett σ values of substituents for *para*- (■) and *meta*- (●) substituted benzaldehydes in *i*PrOH cosolvent. The reported equation refers to the bold line.

The susceptibility of the reaction to the substituents effect is greater for the less reducing and, thus, more selective EtOH radical (ρ = 0.69) than for the *i*PrOH radical (ρ = 0.47). The decreasing reactivity of *meta*- with respect to *para*-substituted benzaldehydes is particularly marked and a separation into two lines may be envisaged: the one corresponding to *meta* substituents (dashed lines in Figures 3 and 4, including benzaldehyde itself) lies appreciably below to the one of *para* substituents.

Since the effect of substituents in the *meta* position are usually used to assess inductive effects, it follows that the increased reactivity of *para*- with respect to *meta* substitution is to be ascribed to the additional resonance stabilization of developing α-hydroxybenzyl radicals **B**$^{\cdot}$.

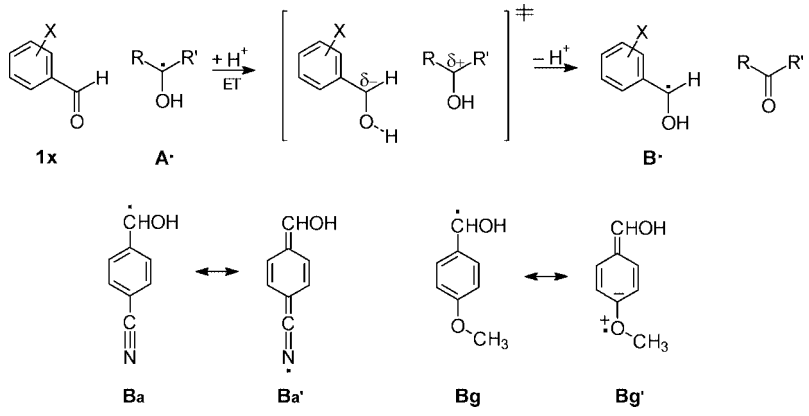
Under the present acidic conditions (pH ≈ 1), the electron transfer step would take place, followed by or concerted with synergic proton transfer, leading to a very fast reaction in which a large degree of radical character is built up in a "late" transition state (Scheme 3). The greater the increase in the radical character, the more resonance stabilizing forms with the unpaired electron spread over the *para* EWG (X = CN, CO_2CH_3, $COCH_3$, Br) contribute to lower the transition-state energy (Scheme 3, structure $\mathbf{B_{a'}}$ shown for X = CN).

This would explain the increased reactivity of *para*- with respect to *meta*-EWG-substituted benzaldehydes, for which resonance stabilized forms of corresponding radical **B** cannot be drawn.[18] The failure of *p*-OCH_3 to correlate well with the other *para* substituents, for example, the low reactivity of *para*-methoxybenzaldehyde (Figures 3 and 4) is in accord with the fact that delocalization of the odd electron onto the oxygen atom results in $\mathbf{B_{g'}}$, which is charge-separated and, consequently, of higher energy than structure $\mathbf{B_{a'}}$.[19]

In addition, whereas $\mathbf{B_a}$ may be regarded as a captodative (cd) radical,[20] which enjoys extra stabilization due the synergic effect of the donor (OH) and of the acceptor substituent (*p*-EWG), $\mathbf{B_g}$ is a didonor (dd) radical for which the effect of the two substituents with like polarity (OH and *p*-OCH_3) is antagonistic, thus destabilizing the radical.[19]

Conclusions

The aqueous Ti^{III}/TBHP system, used in combination with an alcoholic solvent, represents a new, fast, mild, and chemoselective method for promoting reductive pinacolization of aromatic aldehydes. The actual reducing agent is not the metal ion, but rather the α-hydroxyalkyl radical. The higher reactivities of *para*- with respect to *meta*-substituted benzaldehydes are interpreted as being due to the effect of resonance stabilization of the resulting captodative *para*-substituted α-hydroxybenzyl radicals.



Scheme 3. Transition state and resonance structures.

Experimental Section

General: All materials were purchased from commercial suppliers. Liquid benzaldehydes were distilled prior to use. All reactions were performed at room temperature (20 °C) under an atmosphere of nitrogen. NMR spectra were recorded at 500 or 400 MHz for ^{1}H and 125 or 100 MHz for ^{13}C, measured in [D$_6$]DMSO. Chemical shifts (δ) were presented in ppm, using the DMSO peak (δ =2.50 ppm for ^{1}H and 39.43 ppm for ^{13}C) as an internal standard. The ratios of dimers were determined from the intensities of the benzylic protons in the ^{1}H NMR spectra in which the protons of the *dl* isomer appeared at higher field relative to that of the *meso* isomer. ESI-MS were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. The following aqueous solutions were used: a 15% acidic solution of $TiCl_3$ and an 80% solution of TBHP. Flash column chromatography was performed by using 40–63 μm silica gel packing.

Representative Procedure for Pinacol Reaction with $TiCl_3$/TBHP in Aqueous Alcoholic Solution by Using an Excess of Peroxide: To a well-stirred solution of 4-CN-benzaldehyde (**1a**, 262 mg, 2.0 mmol) in EtOH (or *i*PrOH, 10 mL) and $TiCl_3$ (15% aqueous acidic solution, 8.0 mmol, 8.0 mL), at room temp. and under an atmosphere of N_2 was added dropwise a solution of TBHP (80% solution, 5.0 mmol, 0.62 mL) in EtOH (or *i*PrOH, 5.0 mL) over ca. 5 min. The blue color of the reaction mixture discharged and became yellow by the end of the TBHP addition. The alcoholic cosolvent was partially removed in vacuo and the leftover solution was extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude reaction mixture (265 mg) contained pinacols *dl*-**2a** and *meso*-**2a** in a 1:1 ratio according to ^{1}H NMR spectroscopic analysis. Pure pinacols (250 mg, 95%) were obtained by crystallization from EtOAc/hexane (1:1). The same yield was obtained in both EtOH and *i*PrOH cosolvents (Table 1).

Representative Procedure for Pinacol Reaction with $TiCl_3$/TBHP in Aqueous Alcoholic Solution by Using a 1:1 Stoichiometric Amount of TBHP/aldehyde: To a well-stirred solution of 4-CN-benzaldehyde (**1a**, 262 mg, 2.0 mmol) in EtOH (or *i*PrOH, 10 mL) and $TiCl_3$ (15% aqueous acidic solution, 3.0 mmol, 3.0 mL) at room temperature and under an atmosphere of N_2 was added dropwise a solution of TBHP (80% solution, 2.0 mmol, 0.25 mL) in EtOH (or *i*PrOH, 5.0 mL) over ca. 5 min. The reaction mixture changed its color from blue to yellow. However, to ensure the complete decomposition of the peroxide, additional $TiCl_3$ solution (ca. 0.8 mL, 0.8 mmol) was dropped into the reaction mixture in order to barely maintain a pale blue color. Work up was as above. The crude reaction residue, added of a weighed amount of a suitable internal standard (2-CH_3-benzyl alcohol) and analyzed by ^{1}H NMR spectroscopy, revealed **2a** in 77% yield when the reaction was performed in EtOH and 86% yield when *i*PrOH was used, as a 1:1 isomers mixture (Table 2).

Spectroscopic Data: Diols **2a**, **2c**, **2d**, **2e**, **2g**, and **2f** exhibit spectroscopic data consistent with those reported in the literature.[21]

1,2-Bis(3-cyanophenyl)-1,2-ethanediol (*meso*/*dl*) (2a$_m$): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 4.66 (d, s after D_2O exchange, *dl*, *J* = 4.2 Hz, 2 H, 2 × CH), 4.81 (d, s after D_2O exchange, *meso*, *J* = 4.2 Hz, 2 H, 2 × CH), 5.61 (d, D_2O exchangeable, *dl*, 2 H, 2 × OH), 5.66 (d, D_2O exchangeable, *meso*, 2 H, 2 × OH), 7.42–7.70 (m, 8 H *meso* + 8 H *dl*, ArH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 75.3 (*meso*, 2 × CHOH), 75.6 (*dl*, 2 × CHOH), 110.1 (*dl*, 2 × C-CN), 110.3 (*meso*, 2 × C-CN), 118.8 (*meso*, 2 × CN), 118.9 (*dl*, 2 × CN), 128.4, 128.5, 130.38, 130.4, 130.5, 130.8, 131.8, 132.1, (8 × CH *dl* + 8 × CH *meso*), 143.6 (*meso*, 2 × C-CHOH), 144.3 (*dl*, 2 × C-CHOH) ppm. MS (ESI): *m*/*z* (%) = 265 (100) [M + H]$^+$.

1,2-Bis(4-acetylphenyl)-1,2-ethanediol (*meso*/*dl*) (2b): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.52 (*meso*, 6 H, 2 × CH_3), 2.55 (*dl*, 6 H, 2 × CH_3), 3.0–3.5 (*dl* + *meso*, 4 H, 4 × OH), 4.70 (s, *dl*, 2 H, 2 × CH), 4.77 (s, *meso*, 2 H, 2 × CH), 7.29 (d, *meso*, *J* = 8.4 Hz, 4 H, ArH), 7.38 (d, *dl*, *J* = 8.4 Hz, 4 H, ArH), 7.78 (d, *meso*, *J* = 8.4 Hz, 4 H, ArH), 7.85 (d, *dl*, *J* = 8.4 Hz, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 26.48 (*meso*, 2 × CH_3), 26.5 (*dl*, 2 × CH_3), 76.4 (*dl*, 2 × CHOH), 76.5 (*meso*, 2 × CHOH), 127.2 (*dl* + *meso*, 4 × CH), 127.4 (*dl* + *meso*, 4 × CH), 135.4 (*meso*, 2 × C), 135.5 (*dl*, 2 × C), 147.5 (*meso*, 2 × C), 148.3 (*dl*, 2 × C), 197.5 (*meso*, 2 × CO), 194.6 (*dl*, 2 × CO) ppm. MS (ESI): *m*/*z* (%) = 299 (100) [M + H]$^+$.

1,2-Bis(3-acetylphenyl)-1,2-ethanediol (*meso*/*dl*) (2b$_m$): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.46 (s, *meso*, 6 H, 2 × CH_3), 2.53 (s, *meso*, 6 H, 2 × CH_3), 4.70 (d, s after D_2O exchange, *dl*, *J* = 3.3 Hz, 2 H, 2 × CH), 4.79 (d, s after D_2O exchange, *meso*, *J* = 3.3 Hz, 2 H, 2 × CH), 5.41 (d, D_2O exchangeable, *dl*, 2 H, 2 × OH), 5.52 (d, D_2O exchangeable, *meso*, 2 H, 2 × OH), 7.32–7.83 (m, 8 H *dl* + 8 H *meso*, ArH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 26.4 (*meso*, 2 × CH_3), 26.5 (*dl*, 2 × CH_3), 76.4 (*dl*, 2 × CHOH), 76.5 (*meso*, 2 × CHOH), 126.4, 126.6, 126.8, 127.4, 127.5, 131.8, 132.1 (8 × CH *meso* + 8 × CH *dl*), 135.8 (*meso*, 2 × C), 136.0 (*dl*, 2 × C), 142.6 (*meso*, 2 × C), 143.5 (*dl*, 2 × C), 197.7 (*meso*, 2 × CO), 197.8 (*dl*, 2 × CO) ppm. MS (ESI): *m*/*z* (%) = 299 (100) [M + H]$^+$, 281 (50) [M – H_2O + H]$^+$.

Supporting Information (see footnote on the first page of this article): Spectroscopic data for diols **2a$_m$**, **2b**, and **2b$_m$**.

Acknowledgments

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