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The effect of *ortho*-substitution on the efficacy of biphenyls in mediating electron transfer from lithium

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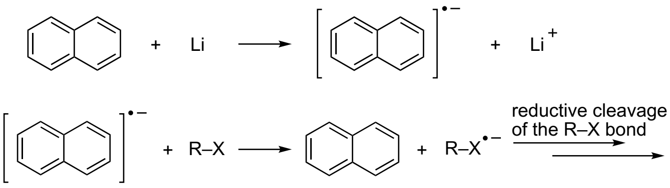
ABSTRACT

A systematic study into the effect of increasing *ortho*-substitution of a range of biphenyls with respect to their ability to mediate electron transfer from lithium metal is described. A synthetic investigation has demonstrated the requirements for effective mediation. The electrochemical reduction of the mediators and of the two substrates was studied in THF, 0.1 M TBAP, at platinum microelectrodes both at room temperature and at low temperature. The formal potentials, E_f^0 extracted from the cyclic voltammograms, are in agreement with results of the synthetic study and computational calculations also provide a correlation.

1. Introduction

Arene-mediated homogeneous electron transfer for the reductive cleavage of functional groups is widely employed in synthetic organic chemistry and is frequently preferred to direct reduction by an alkali metal. Indeed, we have recently explained why biaryl mediated electron transfer from lithium metal is faster than direct reduction in terms of the relative activation energies of the different steps.[1] Typically, lithium metal is reacted with an arene, which may be present in a sub-stoichiometric quantity, and substrate, with the aromatic radical anion being generated in situ (Scheme 1).

In particular, 4,4′-di-*tert*-butyl-1,1′-biphenyl (DBB) has attracted much interest as being one of the most effective mediators for reductive lithiation reactions. Over the past few decades many examples of the use of this mediator have been reported. For example, a range of functional groups, which include thioethers,[2] acetals,[3] tertiary alkyl chlorides[4] and heterocycles[5] have been reduced employing DBB as the mediator; the reductive ring opening of oxygen-containing benzo-fused heterocycles,[6] structural modification of carbohydrates[7] and reductive lithiation of α-amino nitriles[8] have also been reported. In addition, we have investigated a number of applications of DBB-mediated reduction including the total syntheses of (+)-hyacinthacine A_7,[9] and several other pyrrolizidine alkaloids.[10] The formation of enantiopure pyrroline building blocks for natural product synthesis[11] and in the partial reduction of heterocycles[12] has also been achieved.



Scheme 1.

As part of our continuing interest in arene-mediated processes we recently reported a study into why some mediators are more effective reducing agents than others.[13] It was concluded that more reducing radical anions were superior mediators, demonstrated by a comparison of formal potentials and a synthetic study. Herein we describe the results of an investigation to systematically probe the effect of *ortho*-substitution on the ability of a biphenyl to act as an efficient mediator. Detailed synthetic studies and electrochemical measurements of the mediators and substrates are discussed. A computational study is also described so as to provide a comprehensive picture of the influence of *ortho*-substitution and biaryl structure on the ability of an arene to participate in electron transfer from lithium metal.

2. Results and discussion

2.1. Synthetic study

Considering the prototype biphenyl electron transfer mediator, DBB **1**, it was recognised that all analogues would benefit

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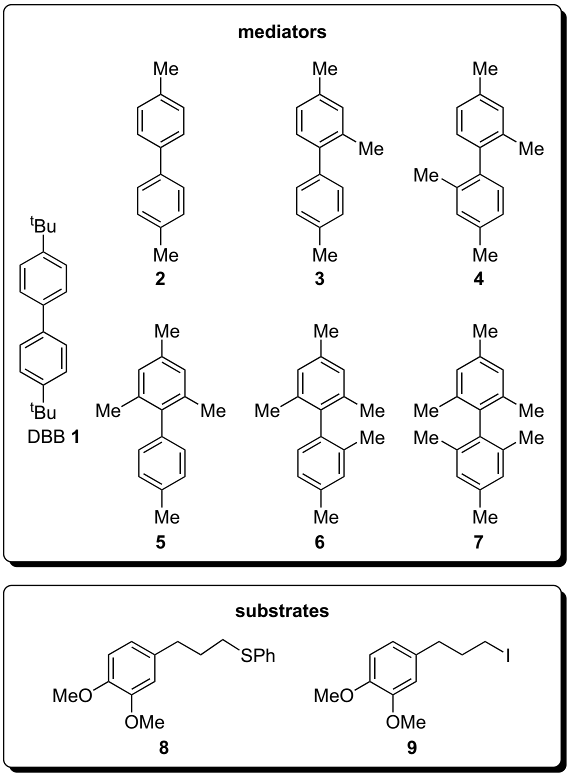
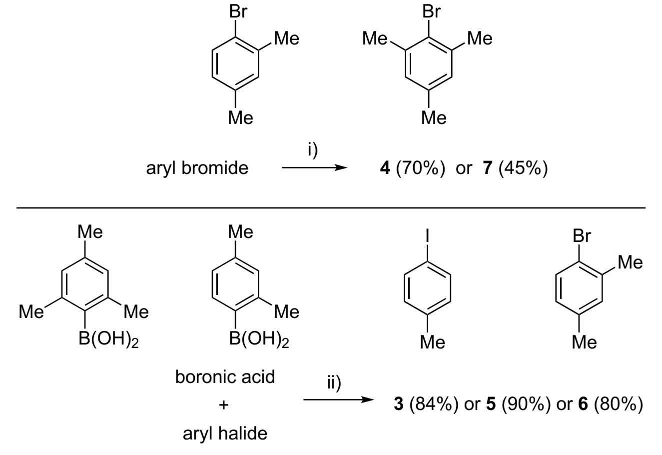
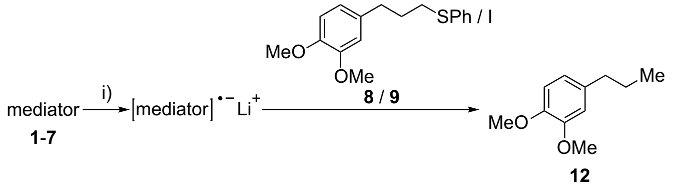


Figure 1. List of proposed mediators and substrates.



Scheme 2. Reagents and conditions: (i) aryl bromide (1 equiv), Mg (5 equiv), THF, 0 °C to reflux, 3 h and then $FeCl_3$ (6 mol %), BIPY (12 mol %), O_2, 30 min; (ii) boronic acid (3 equiv), aryl halide (1 equiv), $Pd(OAc)_2$ (0.4 equiv), P(*o*-tol)$_3$ (0.8 equiv), $Ba(OH)_2 \cdot 8H_2O$ (3.1 equiv), DME/H_2O (6.6:1), reflux, 16 h.

from substitution at the positions *para* to the biaryl bond in order to suppress radical dimerisation during reduction. Thus, a range of biphenyls with increasing substitution at the position *ortho* to the biaryl bond was identified **2**–**7**. Two substrates, which are efficiently reduced by DBB were utilised in this study **8** and **9** (Fig. 1).



Scheme 4. Reagents and conditions: (i) mediator (3 equiv), Li (18 equiv), THF, 0 °C, 3 h and then **8**/**9**, −78 °C, 30 min.

Both DBB **1** and 4,4′-dimethylbiphenyl **2** are commercially available. Biaryls **4** and **7** were synthesised by oxidative dimerisation of the appropriate Grignard reagent[14] and **3**, **5** and **6** were prepared via Suzuki coupling[15] (Scheme 2).

Substrates **8** and **9** were synthesised from a common precursor **11** in two steps from the commercially available alcohol **10**. Mesylation occurred in excellent yield and displacement with thiophenolate generated **8**. Similarly, treatment under Finkelstein conditions furnished iodide **9** (Scheme 3).

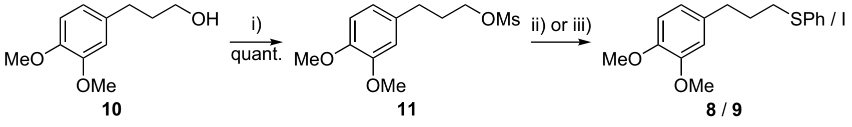
At the outset, it was anticipated that, along with DBB **1**, 4,4′-biphenyl **2** would act as a competent mediator. In addition it was recognised that bimesityl **7** was unlikely to mediate electron transfer; the four *ortho*-substituents would render the phenyl rings orthogonal to one another, preventing any delocalisation. Three key questions were considered:

- At what point would the increased steric congestion at the *ortho* position lead to a cessation of mediation?
- Would there be a gradual decline in mediator ability or would there be an 'all-or-nothing' response?
- Would analytical techniques such as electrochemistry and molecular modelling be able to rationalise, and ultimately predict, the outcome of synthetic studies?

Each potential mediator **2**–**7** and DBB **1** were treated with lithium metal (6 equiv) followed by either phenyl sulfide **8** or iodide **9**. The yield of the corresponding reduced product **12** and/or recovered starting material was then obtained. In addition, a key control experiment was carried out *in the absence of any mediator* to ascertain whether any direct reduction of **8** or **9** by lithium metal was taking place (Scheme 4).

The results of this study are summarised in Table 1. Most importantly, it was demonstrated that direct reduction of the substrates with lithium *was not a competing process* (Table 1, entry 1). Thus, the yields obtained with **1**–**7** would be a true reflection of their efficacy as mediators of electron transfer. Both **2** and **3** acted as competent mediators, giving essentially identical yields of **12** to DBB **1** (Table 1, entries 2–7). In stark contrast, none of **4**–**7** furnished any reduction product (Table 1, entries 8–15), with only starting material being recovered in each case. In all examples the mediator could be recovered in essentially quantitative yield, raising the possibility of developing a catalytic system.[16]

Clearly, more than a single *ortho*-substituent was not tolerated with respect to mediator ability. The fact that the potential mediators gave either comparable results to DBB **1** or no reduction at all was also interesting. In order to probe these empirical observations further, the electrochemical properties of **1**–**7** and **8**,**9** were investigated using both ambient and cryoelectrochemical analysis.



Scheme 3. Reagents and conditions: (i) MsCl, Et_3N, DCM, 0 °C to rt, quant; (ii) PhSH, NaOMe, THF/MeOH (5:1), rt, 92%; (iii) NaI, acetone, rt, 96%.

Table 1
Yields for the sequence depicted in Scheme 2

Entry	Mediator	Substrate	Yield of **12** (%)
1	—	**8**	0[a]
2	**1**	**8**	95
3	**1**	**9**	97
4	**2**	**8**	93
5	**2**	**9**	93
6	**3**	**8**	93
7	**3**	**9**	94
8	**4**	**8**	0[a]
9	**4**	**9**	0[a]
10	**5**	**8**	0[a]
11	**5**	**9**	0[a]
12	**6**	**8**	0[a]
13	**6**	**9**	0[a]
14	**7**	**8**	0[a]
15	**7**	**9**	0[a]

[a] Quantitative recovery of starting material.

2.2. Electrochemical study

Over the past few years, our laboratories have focused on the development of electrochemical studies that are undertaken under similar conditions to arene-mediated electron transfer from lithium reactions in THF at low temperature. Electrochemical studies allow access to many physical parameters that are useful in understanding how a molecule will react. Using THF as the electrolyte solvent is particularly interesting in regard of the large cathodic potential window available for electrochemical measurements.[1,13,17–21] In contrast to macroelectrodes, microelectrodes allow the acquisition of voltammograms that are negligibly affected by the high resistivity of the medium.[21,22] Moreover, by working at low temperature both the electron transfer kinetics and reaction kinetics are attenuated thus allowing more insight into the mechanisms that are involved.[17,18] These electrochemical studies show, in this case, an agreement between the solution electron transfer results and intrinsic physical parameters.

2.2.1. Electrochemical studies of the mediators at room temperature

The electrochemical reduction of the mediators was studied in THF, 0.1 M tetrabutylammonium perchlorate (TBAP), at platinum microelectrodes. The biaryl/biaryl radical anions were found to be chemically reversible for compounds **1**–**3** while for compounds **4**–**7** no peak or wave could be observed within the potential window defined by the solvent electrolysis. No following or preceding

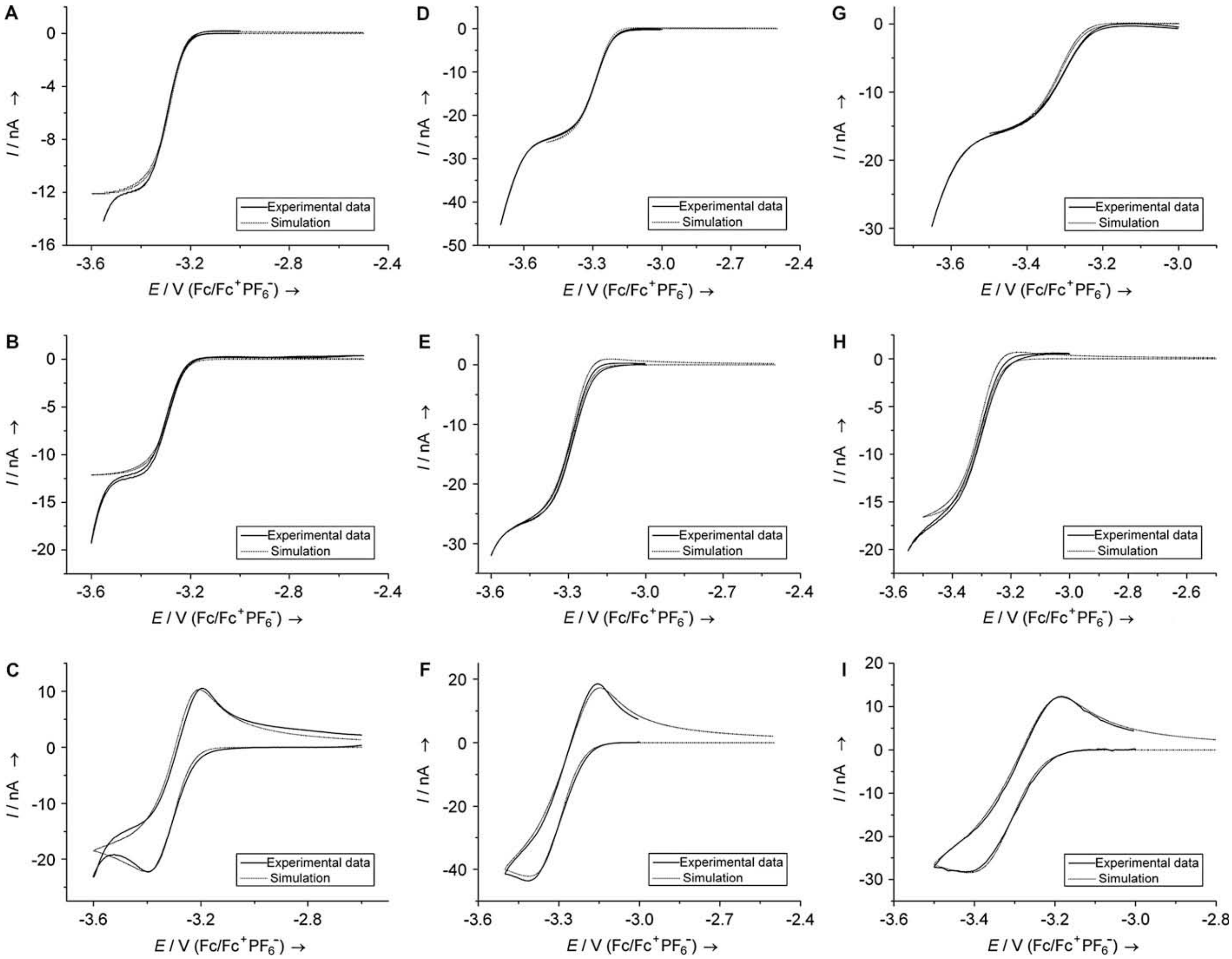


Figure 2. Experimental (solid line) and theoretical (dotted line) voltammograms for the reduction of **1**, **2** and **3** in THF, 0.1 M TBAP, obtained at 293 K at a 10 μm diameter Pt disc microelectrode at various scan rates. (A), (B) and (C) correspond to voltammograms obtained for compound **1**, 4.98 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}. (D), (E) and (F) correspond to voltammograms obtained for compound **2**, 7.5 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}. (G), (H) and (I) correspond to voltammograms obtained for compound **3**, 6.38 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}.

Table 2
Values of the diffusion coefficient, D, of the heterogeneous kinetic constant, k_0, and of the formal potential, E_f^0, for the biphenyls at 293 K, obtained from the modelling of the cyclic voltammograms obtained at a 10 μm disc platinum microelectrode in THF, 0.1 M TBAP

Compound	$D_A/10^{-5}$ cm^2 s^{-1}	$D_B/10^{-5}$ cm^2 s^{-1}	k_0/cm s^{-1}	E_f^0/V	α
1[a]	1.15±0.1	0.46±0.05	0.030±0.001	−3.27±0.03	0.5±0.05
2	1.75±0.1	0.30±0.05	0.016±0.001	−3.22±0.03	0.5±0.05
3	1.26±0.1	0.25±0.05	0.018±0.001	−3.25±0.03	0.5±0.05

[a] Values concerning compound **1** are reported from Ref. 1.

chemical reaction was observed for any of the mediators. The cyclic voltammograms were modelled allowing the determination of the diffusion coefficient of the biaryl, D_A, of the diffusion coefficient of the biaryl radical anion, D_B, of the formal potential, E_f^0, of the transfer coefficient, α, and of the standard heterogeneous kinetic constant for the electron transfer, k_0 within the Butler–Volner formalism.

In practice the three voltammograms obtained at 0.01, 0.1 and 20 V s^{-1} were fitted for **2** and **3**. Similar studies had been performed previously for compound **1**.[1] Figure 2 shows the experimental and the modelled voltammograms that were obtained for **1**, **2** and **3**. It is clear that an acceptable fitting of the experimental curves can be obtained over a wide range of scan rates. The values of the physical parameters extracted are reported in Table 2.

The difference between D_A and D_B shows that the biphenyl radical anion that is generated diffuses much more slowly than the biphenyl molecule. We explain this phenomenon by the occurrence of an ion pairing between the biphenyl parent radical anion and the *tert*-butylammonium cation used as an electrolyte ion in the solution.[21] It can be also observed that compounds **1**, **2** and **3** have very similar values of the formal potential, E_f^0, which relates to their similar thermodynamic capacity in accepting an electron and which is in agreement with the synthetic studies.

2.2.2. *Electrochemical studies of the mediators at low temperature (cryoelectrochemistry)*

In order to accurately model conditions that are used for synthetic solution electron transfer studies, the electrochemical studies were performed at low temperature, 192 K (Fig. 3).

Again, well defined electrochemical waves and peaks could be observed for compounds **1**–**3**. However, no peak or wave could be properly observed for potential mediators **4**–**7** although the beginning of a signal could be observed just before the limit of the

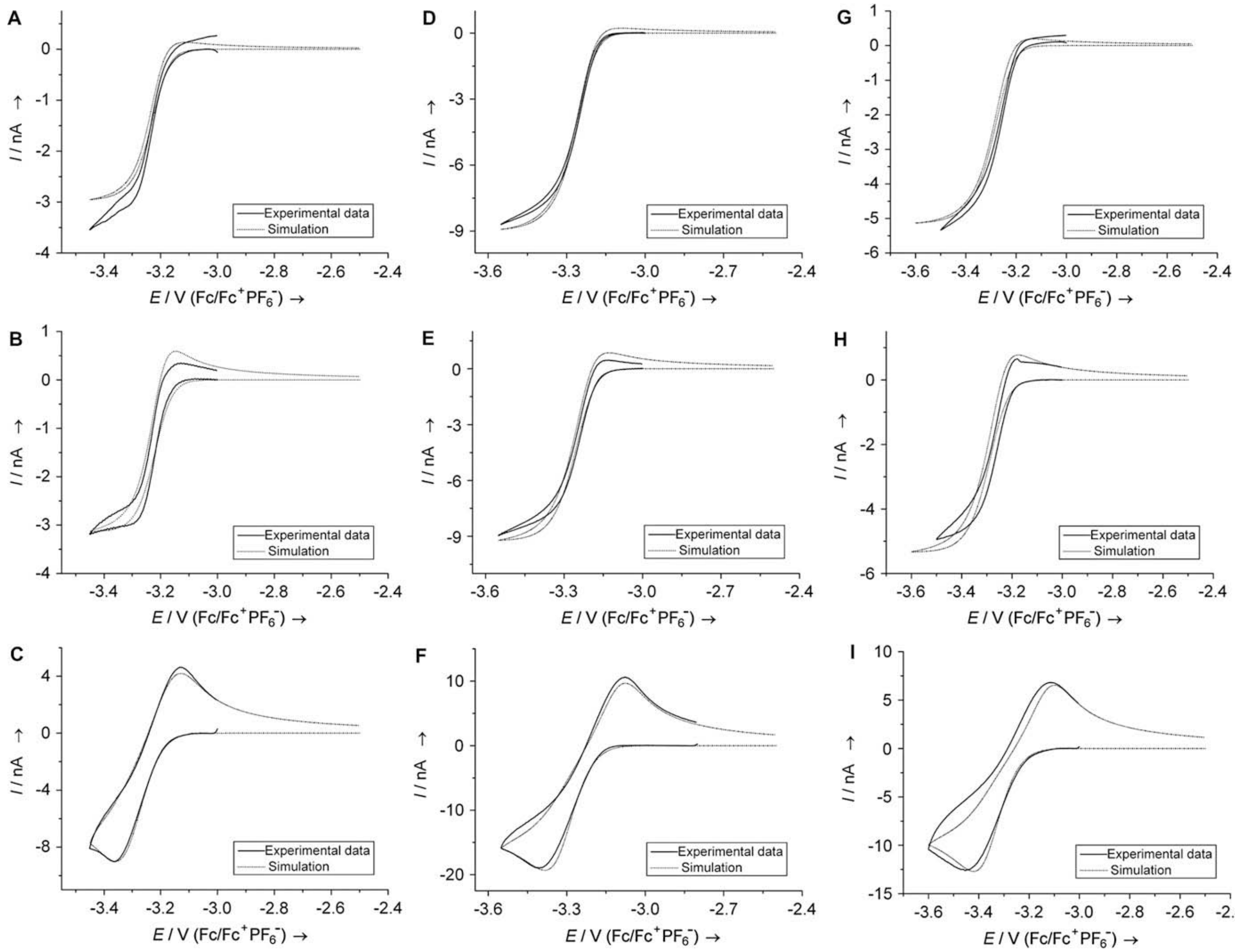


Figure 3. Experimental (solid line) and theoretical (dotted line) voltammograms for the reduction of **1**, **2** and **3** in THF, 0.1 M TBAP, obtained at 192 K at a 10 μm diameter Pt disc microelectrode at various scan rates. (A), (B) and (C) correspond to voltammograms obtained for compound **1**, 4.98 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}. (D), (E) and (F) correspond to voltammograms obtained for compound **2**, 7.5 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}. (G), (H) and (I) correspond to voltammograms obtained for compound **3**, 6.38 mM, respectively, at 0.01, 0.1 and 20 V s^{-1}.

Table 3
Values of the diffusion coefficient, D, of the heterogeneous kinetic constant, k_0, and of the formal potential, E_f^0, for the mediators at 192 K, obtained from the modelling of the cyclic voltammograms obtained at a 10 μm disc platinum microelectrode in THF, 0.1 M TBAP

Compound	$D_A/10^{-5}$ $cm^2\,s^{-1}$	$D_B/10^{-5}$ $cm^2\,s^{-1}$	k_0/cm s^{-1}	E_f^0/V	α
1[a]	0.27±0.1	0.03±0.01	0.005±0.001	−3.20±0.03	0.5±0.05
2	0.58±0.1	0.07±0.01	0.005±0.001	−3.18±0.03	0.5±0.05
3	0.39±0.1	0.04±0.01	0.003±0.001	−3.21±0.03	0.5±0.05

[a] Values concerning compound **1** are reported from Ref. 1.

potential window. The values of the physical parameters extracted for the modelling of the voltammograms for compounds **1**–**3** are reported in Table 3.

As far as compounds **4**–**7** are concerned, it could be concluded from the experimental curves, that the values of their formal potential, E_f^0, are more negative than −3.6 V/(Fc/Fc$^+$ PF$_6^-$). As far as the reduction of Li$^+$ is concerned values of E_f^0 that were obtained in previous studies were −3.48 and −3.43 V/(Fc/Fc$^+$ PF$_6^-$), respectively, at 295 and 243 K.[23] It is possible to estimate the value of E_f^0 at 192 K to be −3.38 V/(Fc/Fc$^+$ PF$_6^-$) by extrapolation. It is then clear that the 'reducing power' of lithium is sufficient to proceed to an electron exchange with compounds **1**, **2** and **3** but *not* with **4**–**7**, presumably due to their being little conjugation between the two rings.

2.2.3. *Electrochemical studies of the substrates*

The cyclic voltammetry of compound **8** shows that, while the curves obtained are not well resolved at 298 K (because its reduction takes place at close proximity to the limit of the potential window), well defined voltammograms are obtained at 192 K (Fig. 4).

This illustrates the fact, as previously described, that a wider potential window is obtained when working at low temperature and consequently certain substrates that could not be studied at room temperature can be studied when using cryoelectrochemical techniques. Compound **8** is irreversibly reduced and its reduction starts at a potential of −3.5 V/(Fc/Fc$^+$ PF$_6^-$) at 192 K. Its reduction is believed to involve an irreversible, dissociative, two electron transfer and its thermodynamic formal potential will be lower than the kinetically controlled potential at which the reduction can actually be observed and hence the formal potential of **8** will be more negative than the formal potential of compounds **1**, **2** and **3**. The reduction of compound **9** starts at −2.7 V/(Fc/Fc$^+$ PF$_6^-$) and exhibits a strong absorption onto the electrode upon reduction rendering the voltammogram poorly resolved. It can be concluded from these data that the radical anions corresponding to compounds **1**, **2** and **3** are potentially good electron donors for substrates **8** and **9** for which the direct reduction is slow (kinetically controlled).

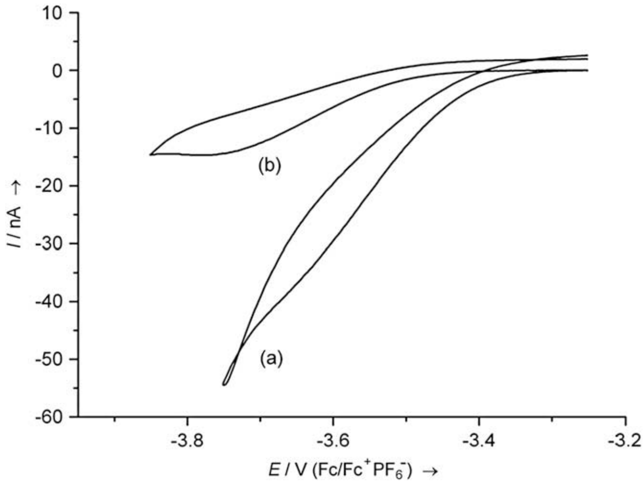


Figure 4. Voltammograms corresponding to the reduction of compound **8**, 5.83 mM, in THF, 0.1 M TBAP, obtained at a 10 μm diameter Pt disc microelectrode at 20 V s^{-1}; curve (a) was recorded at 298 K and curve (b) at 192 K.

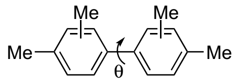


Figure 5. Dihedral angle, θ.

These electrochemical studies confirm that mediators **1**–**3** are well suited both for the heterogeneous electron transfer from lithium and for the homogeneous electron transfer to the chosen substrates. In agreement with the solution electron transfer experiments, it was also found that the formal potentials, E_f^0, of compounds **4**–**7** are too negative to allow any of the heterogeneous and homogeneous electron transfers cited above.

2.3. Computational study

Having successfully correlated the synthetic observations with electrochemical analysis of both the potential mediators and substrates, a computational study was undertaken. It seemed likely that the dihedral angle, θ, between the two rings would provide useful information regarding the ability of a potential mediator to transfer an electron from lithium metal (Fig. 5).

It has been shown that the conformation of substituted biphenyls will be determined predominately by two factors:[24]

- π-delocalisation between both rings;
- coulombic repulsion between the *ortho*-substituents.

Conformational analyses of biphenyl have been the subject of several investigations; in the gas phase it has been demonstrated that the dihedral angle, θ, between the two rings is 42°,[25] and in solution a value of θ of 32° has been found.[26] However, the crystal structure of biphenyl indicates that the molecule is completely planar.[27] In contrast, DBB **1** has been shown to have essentially the same conformation in both the gas and crystalline phase, with a value of θ of about 40°.[28] This is presumably due to the steric bulk of the *tert*-butyl groups disrupting crystal packing to some extent, preventing the molecule becoming planar. Thus, it seems likely that the planar conformation of biphenyl in the crystalline phase is due to packing effects.

Although several investigations into the effect of *ortho*-substitution on the conformation of biphenyls have been detailed,[29] a systematic study of this kind has yet to be reported. Minimum energy calculations, to determine the value of θ for DBB **1** and biphenyls **2**–**7**, were performed using the Hartree-Fock 6-31G*

Table 4
Calculated dihedral angle (θ)

Entry	Biphenyl	Dihedral angle, θ (°)
1	**1**	40
2	**2**	40
3	**3**	53
4	**4**	88
5	**5**	89
6	**6**	90
7	**7**	90

method as implemented in Spartan'08. The geometry was optimised at 10° intervals, including all the degrees of freedom except the dihedral angle θ. The resulting rotational potential curves were analysed to determine the value of θ corresponding to the minimum energy. The results are summarised in Table 4.

Calculated dihedral angles of ca. 90° for **4**–**7** correlate to those biphenyls that were not competent mediators (Table 2, entries 4–7). The calculations for θ of both DBB **1** and its dimethyl congener **2** were in accordance with literature values[28] and **3**, with one *ortho*-substituent had a value of θ of 53° (Table 2, entries 1–3). It should be noted, however, that these calculations were performed on the neutral species and the conformation of the corresponding radical anion may not correlate.[30] Nevertheless, it seems likely that these values offer a qualitative analysis of the effect of *ortho*-substitution on the ability of biphenyls to act as mediators of electron transfer; a calculated dihedral angles that approaches 90° is a good indicator that the biphenyl will not be able to transfer an electron easily from lithium metal surface. This implies that efficient conjugation between the two rings is necessary for a biphenyl to be an effective mediator of electron transfer.

3. Conclusions

DBB **1** and biphenyls **2** and **3** are effective mediators of electron transfer from lithium metal, with little difference in performance in the synthetic study. Electrochemical measurements are in agreement with this observation and indicate that all have very similar formal potentials, E_f^0. Similarly, biphenyls **4**–**7** have electrochemical potentials, which should render them ineffective mediators—a result borne out in the synthetic investigation. Considering the dihedral angle, θ, of **1**–**7** as an indicator of mediator competency has also been shown to be in general agreement with our observations.

4. Experimental

4.1. General procedures and methods

Unless otherwise specified, all reactions were carried out under an atmosphere of argon. Tetrahydrofuran (THF) was purified by filtration through two columns of activated alumina (grade DD-2) as supplied by Alcoa, employing the method of Grubbs.[31] Acetonitrile, dichloromethane and toluene were dried by passing through activated alumina columns (activated basic aluminium oxide, Brockmann I, standard grade, ~150 mesh, 58 Å) as supplied by Aldrich. Methanol was purified by distillation over calcium hydride, and stored over molecular sieves (4 Å). Other solvents were used as supplied without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on aluminium plates pre-coated with Merck silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (4.3–6.3 μm). Melting points were recorded using a Leica VMTG heated-stage microscope and are uncorrected. Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer, as a thin film between NaCl plates or as a KBr disc. Proton (^{1}H) and carbon (^{13}C) NMR were recorded using a Bruker AV400 (400 MHz and 100 MHz). Mass spectra (m/z) and accurate mass (HRMS) were recorded on an Agilent 6890 Series GC system for chemical ionisation (CI) and on a Fisons Platform II for electrospray ionisation (ESI).

4.1.1. Oxidative dimerisation of Grignard reagents

The aryl bromide (1 equiv) was added to a mixture of magnesium turnings (5 equiv), I_2 (one crystal) and THF (5 mL/mmol) at 0 °C. The reaction mixture was heated at reflux for 3 h and then allowed to cool to room temperature. The solution was transferred via cannula to a flame-dried Schlenk tube containing $FeCl_3$ (6 mol %) and 2,2′-bipyridine (12 mol %) in THF (5 mL/mmol). The vessel was evacuated and back filled with oxygen three times and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate (10 mL/mmol) and adsorbed onto SiO_2. Purification by flash column chromatography (SiO_2; petroleum ether) gave the desired compounds in between 80 and 90% yield. ^{1}H and ^{13}C NMR spectra of **4** and **7** were in accord with literature values.[32,33]

4.1.2. Suzuki coupling

A solution of the appropriate boronic acid (3 equiv), aryl halide (1 equiv), $Pd(OAc)_2$ (0.4 equiv), P(*o*-tol)$_3$ (0.8 equiv) and $Ba(OH)_2\cdot 8H_2O$ (3.1 equiv) in a mixture of dimethoxyethane and water (6.6:1; 10 mL/mmol) was heated at 50 °C for 16 h. The reaction mixture was washed with saturated aqueous NH_4Cl (10 mL/mmol) and then filtered through a pad of Celite, washing with diethyl ether. The filtrate was concentrated in vacuo and purified by flash column chromatography (SiO_2; petroleum ether) to give the desired compounds in between 40 and 70% yield. ^{1}H and ^{13}C NMR spectra of **3**, **5** and **6** were in accord with literature values.[34–36]

4.1.3. Syntheses of substrates **8** and **9**

*4.1.3.1. Synthesis of mesylate **11**.* Methanesulfonyl chloride (10.1 mL, 130 mmol) was added dropwise to a solution of triethylamine (21 mL, 153 mmol) and 3-(3′,4′-dimethoxyphenyl)-1-propanol (10 g, 52 mmol) in CH_2Cl_2 (170 mL) at 0 °C. The resulting yellow suspension was stirred at room temperature for 2 h and then quenched by addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). The resulting biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to yield mesylate **11** (14 g, 100%), which was sufficiently pure to be used directly.

*4.1.3.2. Synthesis of **8**.* Thiophenol (8.5 mL, 83.0 mmol) was added to a solution of $NaOCH_3$ (4.5 g, 83.0 mmol) in THF/CH_3OH (5:1; 25 mL) at room temperature. The reaction was stirred at room temperature for 30 min and then a solution of mesylate **11** (3.5 g, 12.8 mmol) in THF/CH_3OH (5:1; 11 mL) was added. The reaction mixture was stirred at room temperature for 16 h and then quenched by addition of a saturated aqueous solution of NH_4Cl and the product was extracted with diethyl ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2; petroleum ether to petroleum ether/diethyl ether; 9:1) yielded **8** (3.4 g, 92%) as a colourless solid. Mp 75–78 °C; ν_{max} (KBr disc)/cm^{-1} 2997, 2934, 2833, 1589, 1515, 1480, 1463, 1264, 1236, 1156, 1029; δ_H (400 MHz; $CDCl_3$) 7.34–7.26 (4H, m, 4×Ar*H*), 7.20–7.16 (1H, m, 1×Ar*H*), 6.74–6.71 (2H, m, 2×Ar*H*), 3.87 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 2.93 (2H, t, *J* 7.2, C(3′)*H*$_2$), 2.73 (2H, t, *J* 7.2, C(1′)*H*$_2$), 1.97 (2H, ~quintet, *J* 7.2, C(1′)*H*$_2$); δ_C (100 MHz; $CDCl_3$) 148.7, 147.1, 136.5, 133.7, 128.9, 128.7, 125.7, 120.2, 111.6, 111.0, 55.8, 55.7, 34.1, 32.6, 30.6; m/z (ESI) 311 ([M+Na]$^+$, 100%); HRMS (ESI) $C_{17}H_{20}O_2SNa$ ([M+Na]$^+$) requires 311.1082, found 311.1074.

*4.1.3.3. Synthesis of **9**.* NaI (9.6 g, 63.9 mmol) was added to a solution of mesylate **11** (3.5 g, 12.8 mmol) in acetone (36 mL). The resulting suspension was stirred at room temperature for 16 h and then filtered through a pad of Celite and concentrated in vacuo. Purification by flash column chromatography (SiO_2; petroleum ether/diethyl ether; 9:1) yielded **9** (3.7 g, 96%) as a pale yellow oil. ν_{max} (film)/cm^{-1} 2933, 2832, 1590, 1516, 1464, 1418, 1262, 1237, 1157, 1029; δ_H (400 MHz; $CDCl_3$) 6.79 (1H, d, *J* 8.0, 1×ArH), 6.74–6.72 (2H, m, 2×Ar*H*), 3.87 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.16 (2H, t, *J* 7.0, C(3′)*H*$_2$), 2.67 (2H, t, *J* 7.0, C(1′)*H*$_2$), 2.10 (2H, ~quintet, *J* 7.0, C(1′)H_2); δ_C (100 MHz; $CDCl_3$) 148.7, 147.1, 132.8, 120.3, 111.7, 111.1, 55.8, 55.7, 35.6, 34.9, 6.5; m/z (ESI) 329 ($[M+Na]^+$, 100%); HRMS (ESI) $C_{11}H_{15}IO_2Na$ ($[M+Na]^+$) requires 329.0014, found 329.0015.

4.1.4. Mediated reductions

Lithium metal (18 equiv) was added to a solution of the appropriate mediator (3 equiv) in THF (100 mL/mmol) in a flame-dried Schenk tube under a constant flow of argon at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then cooled to –78 °C. A pre-cooled (–78 °C) solution of either **8** or **9** (1 equiv) in THF (10 mL/mmol) was and then added via cannula and the reaction mixture was stirred at –78 °C for 30 min. The reaction was quenched by transfer via cannula to a saturated aqueous solution of NH_4Cl (50 mL/mmol) and the product was extracted with diethyl ether (3×20 mL/mmol). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The mixture was purified by flash column chromatography (SiO_2; petroleum ether to petroleum ether/diethyl ether; 9:1).

4.2. Electrochemical measurements

4.2.1. Chemicals used for the electrochemical measurements

Ferrocene (Aldrich, purum, 98 wt %), ferrocenium hexafluorophosphate (Aldrich, 98 wt %) and tetrabutylammonium hexafluorophosphate (Aldrich, 98 wt %) were used as received. Tetrabutylammonium perchlorate (Alfa Aesar, Heysham, UK, electrochemical grade) was purified following a literature protocol.[37] Argon (BOC Gases, Guilford, UK, pureshield) was used for degassing.

4.2.2. Electrochemical instrumentation and procedures

The electrochemical investigations were achieved using an Eco Chemie PGSTAT20 potentiostat (Eco Chemie, Utrecht, Netherlands). The electrochemical cell used was a standard airtight standard three-electrode cell. The working microdisc electrode was a 10 μm diameter Pt electrode (Cypress Systems Inc., Kansas, USA). The auxiliary electrode was a 0.5 mm diameter platinum wire (Goodfellow Cambridge Ltd., Cambridge, UK). The reference electrode used was a ferrocene/ferrocenium hexafluorophosphate (Fc/$Fc^+PF_6^-$) that was specifically designed for cryoelectrochemical experiments in THF.[20] The setup consists in a platinum wire dipping in a 4 mM equimolar ferrocene/ferrocenium ion hexafluorophosphate and 0.1 M tetra *n*-butylammonium hexafluorophosphate, TBAF, solution in THF. The reference is separated from the cell solution compartment by a porous frit.

The cleaning of the microdisc electrode consisted in polishing the surface of the electrode on a clean polishing pad (Kemet, UK) using 1.0 μm and 0.3 μm aqueous alumina slurries (Beuhler, Lake Buff, IL, USA), and subsequently rinsed in de-ionised and doubly filtered water. The electrodes were oven-dried and cooled in a desiccator over silica gel crystals prior to use. Before carrying out electrochemical experiments in THF, the microdisc radius was calibrated by recording a voltammogram at 0.01 V s^{-1} in a 3 mM ferrocene and 0.1 M TBAF acetonitrile solution.

Specific care has to be given to avoid the presence of water traces in the cell. Flasks containing the electrolytic salt were kept 12 h at 100 °C in an oven and subsequently put under vacuum for 4 h before use. Syringes and needles, used for the transfer of reagents or the electrolytic solution, were oven-dried at 100 °C and cooled in a desiccator over silica gel crystals. The solutions were degassed with argon for 3 min to remove any trace of oxygen and an inert argon atmosphere was maintained throughout all analyses. The argon was dried by passing through a pure sulfuric acid solution and then trough a silica gel column. All electrochemical experiments were run within a Faraday cage.

For cryoelectrochemical measurements, the electrochemical cell was immersed in an ethanol bath thermostated by a Julabo FT902 Immersion cooler.

4.2.3. Fitting of experimental voltammograms

Experimental voltammograms obtained at macroelectrodes were modelled using the software Digisim®. Experimental voltammograms obtained at microelectrodes were modelled using a simulation program developed in our laboratory.[38]

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