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Intermolecular oxidative dehydrogenative 3,3'-coupling of benzo[*b*]furans and benzo[*b*]thiophenes promoted by DDQ/H⁺: total synthesis of shandougenine B†‡

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With an excess of a strong acid, 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) is shown to promote metal-free intermolecular oxidative dehydrogenative (ODH) 3,3'-coupling of 2-aryl-benzo[*b*]furans and 2-aryl-benzo[*b*]thiophenes up to 92% yield as demonstrated with 9 substrates. Based on the analysis of oxidation potentials and molecular orbitals combined with EPR, NMR and UV-Vis observations, the studied reaction is initiated by a DDQ-substrate charge transfer complex and presumably proceeds *via* oxidation of the substrate into an electrophilic radical cation that further reacts with another molecule of a neutral substrate. The coupling reactivity can easily be predicted from the oxidation potential of the substrate and the morphology of its frontier molecular orbitals. The intermolecular ODH coupling reaction allowed a concise total synthesis of the natural product shandougenine B.

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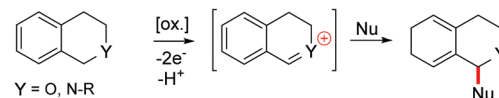
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Introduction

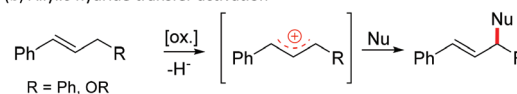
Quinones are important oxidizers in both biological and synthetic chemical conversions.¹ For example, the high oxidative power of 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) makes it a frequently used oxidant in various chemical conversions. Broadly categorizing, there are three commonly accepted mechanistic pathways associated with oxidation: hydride abstraction, hydrogen atom transfer and single electron transfer (SET).²

It has previously been shown that quinone promoted heteroatomic oxidations associated with α -deprotonation (Scheme 1a) or direct hydride transfer (Scheme 1b) lead to the formation of good electrophiles (*e.g.* iminium, oxonium or allylic cations) that can be coupled with various nucleophiles (Nu).^{3,4} Similarly, an electrophile can be generated by one electron oxidation of a neutral substrate into a radical cation

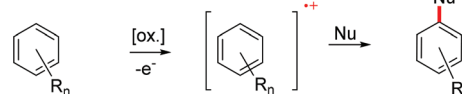
(a) Two electron oxidation iminium/oxonium pathway



(b) Allylic hydride transfer activation



(c) Single-electron transfer radical cation formation



Scheme 1 Quinone mediated metal-free approaches for intermolecular oxidative dehydrogenative (ODH) couplings.

that can subsequently react with different nucleophiles such as water or aryl (Scheme 1c).^{3,5,6a} The last mechanistic pathway operates in many quinone mediated intramolecular oxidative couplings of aryls, but reports on analogous intermolecular couplings are quite rare.^{3,6a-c} Common to these reactions is that quinones are used in the presence of a strong acid promotor (*e.g.* TFA, MsOH, H₂SO₄, TfOH, HClO₄ or HFSO₃), which has been shown to increase the oxidative power of the quinone considerably.⁶

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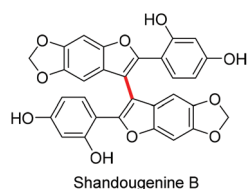
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† This paper is dedicated to Professor Ari M. P. Koskinen on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Crystallographic data, xyz-coordinates, cyclic voltammetry data and EPR, ¹H and ¹³C NMR spectra (PDF). And X-ray crystallographic data for DDQ: 1c (1:2) complex (CIF). CCDC 1477482 (1c-DDQ). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6qo00331a

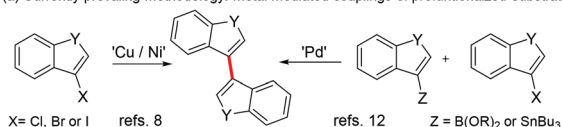


Numerous synthetic methods have been used to construct the 3,3'-bibenzo[*b*]furan and 3,3'-bibenzo[*b*]thiophene skeletons intermolecularly.^{7–13} This structural motif is found in natural products,¹⁴ diphosphine metal ligands,^{7a,8a,b} diphosphine oxide organocatalysts¹⁵ and in organic chiral electrodes.¹⁶ Nevertheless, many of the modern high yielding coupling methods require the use of prefunctionalized starting materials, stoichiometric or substoichiometric amounts of transition metals or air sensitive or pyrophoric reagents (Scheme 2a). However, benzo[*b*]furans and benzo[*b*]thiophenes can be 3,3'-coupled from unfunctionalized monomers directly by the Brønsted acid mediated Friedel–Crafts reaction to dihydro-3,3'-benzofused intermediates in variable yields (Scheme 2b).^{10,17} The McMurry coupling of 3-oxobenzofurans has also been shown to offer a viable route to dihydrogenated intermediates (Scheme 2b).⁷ These intermediates can then be dehydrogenated either thermally (Friedel–Crafts) or with a stoichiometric amount of an oxidant such as DDQ (McMurry).

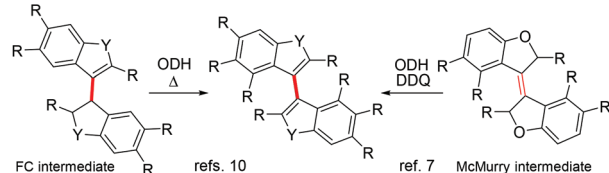


In our previous studies, we have observed that carbonyl rich heterogeneous carbon materials can catalyze the oxidative coupling of various unfunctionalized benzo-fused heterocycles.¹⁸ In that paper, we also observed that DDQ is capable of mediating a similar 3,3'-homocoupling of 2-phenyl-benzo[*b*]furan in the presence of MsOH.^{18b} Herein we report the optimization of the synthetic procedure, the study of the reaction scope and an improved understanding of the reaction mechanism.

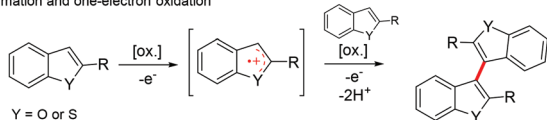
(a) Currently prevailing methodology: metal mediated couplings of prefunctionalized substrates



(b) Examples of oxidative dehydrocoupling of dihydro benzo[*b*](thio)furan intermediates: two step routes initiated with Friedel–Crafts (FC) or McMurry coupling



(c) This work: DDQ mediated coupling via consecutive one-electron oxidation, C–C bond formation and one-electron oxidation



Scheme 2 Various synthetic routes to 3,3'-bibenzo[*b*]furan and 3,3'-bibenzo[*b*]thiophene skeletons.

ism *via* experimental and computational studies (Scheme 2c). We also demonstrate the usefulness of the devised method in the first total synthesis of the 3,3'-bibenzo[*b*]furan natural product, shandougenine B.^{14b}

Results and discussion

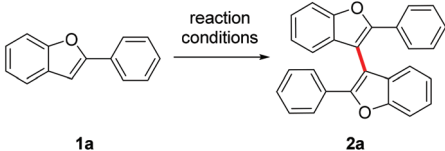
We began the development of our method with non-optimized reaction conditions, 1 eq. of DDQ, 5 eq. of MsOH and 1 eq. of **1a** in DCM (0.05 M) at RT, which yielded 2,2'-bis(phenyl)-3,3'-bibenzo[*b*]furan **2a** in 61% yield in 1 h.^{18b} In preliminary studies, we found that an acid additive was necessary for the progress of the reaction. Therefore, we tested the effect of several acids on the reaction and found that, out of these, only MsOH worked satisfactorily (Table 1, entries 1–3, see the ESI† for kinetic data). Later we noticed that the behaviour of TFA was both concentration and substrate dependent. At higher concentrations TFA could promote the reaction of **1a** to **2a**, whereas in more dilute solutions it promoted the coupling of the more electron rich substrate **1c** to **2c**.¹⁹ Next, we screened solvents and found that DCE worked better than DCM or CHCl₃, and that MeNO₂ gave a low yield (Table 1, entries 3–6). We then employed a two level full factorial design for three factors to optimize the reaction conditions.²⁰ Entry 3 was chosen as the centre point and molarity, temperature and the amount of DDQ were set as variables (Table 1, entries 3 and 7–14). One corner of the screened reaction space (+1, –1, –1) gave a very high (99%) yield (entry 11) and no further optimization was deemed necessary.²¹

After determining the optimized reaction conditions, the scope of the reaction was studied next. In the case of 2-aryl-benzo[*b*]furans, we were able to obtain the corresponding 2,2'-bis(aryl)-3,3'-bibenzo[*b*]furans in good to excellent isolated yields (Scheme 3, **2a–c**). A slightly lower yield (68%) of the coupling product **2d** was obtained when the 2-aryl substituent was functionalized with an amide group at the *para*-position. However, the electron poor 2-(4-nitrophenyl)benzo[*b*]furan **1i** could not be coupled even in the presence of a stronger acid TfOH or with different oxidants such as *p*-tetrachloro-*o*-quinone or ammonium persulfate (see below). To our pleasure, we could, however, obtain the corresponding 2,2'-bis(aryl)-3,3'-bibenzo[*b*]thiophenes, **2e–g**, in equally high yields as the related bibenzo[*b*]furans **2a–c**. Undesirably, the 3,3'-homocoupling product **2h**, 2,2'-bis(2-thienyl)-3,3'-bibenzo[*b*]thiophene was obtained only in 14% yield. We believe that the reason for such a low yield is in the structure of **1h** that enables reactivity at two sites, benzo[*b*]thiophene 3- and thiophene 5-positions, leading to oligomerization. The oxidative 3,3'-homocoupling of the electron rich substrate **1j** would have given a direct route to the natural product kynapcin-24,^{14a} but we could not obtain any product under the reaction conditions employed (see below).

Based on previous studies,⁶ it seemed reasonable that the reactions are initiated by a SET between the substrate and the DDQ/H⁺ and the oxidation potential of a particular substrate

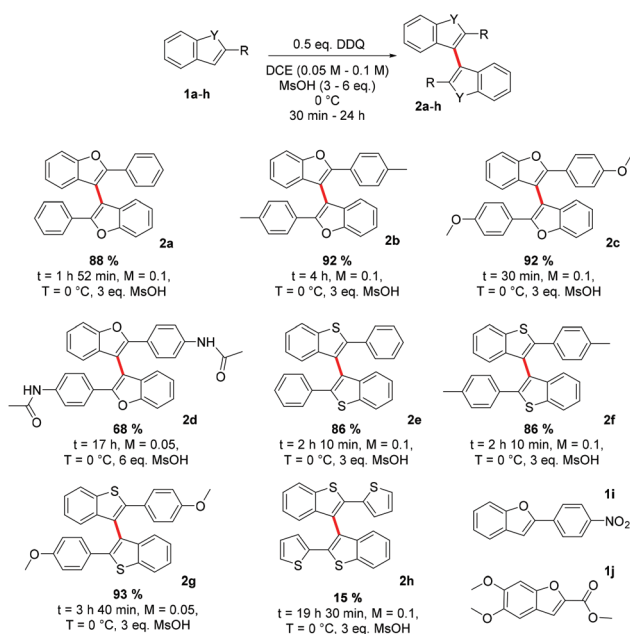


Table 1 Optimization of reaction conditions



Entry	Solvent (molarity)	T (°C)	Time (h)	Acid additive (3 eq.)	Amount of DDQ (eq.)	NMR yield ^a (%)
1	DCM (0.05)	RT	O/N	TFA	1	n.r.
2	DCM (0.05)	RT	O/N	Sc(OTf) ₃	1	n.r.
3	DCM (0.05)	RT	O/N	MsOH	1	75
4	CHCl ₃ (0.05)	RT	1.5	MsOH	1	56
5	DCE (0.05)	RT	1.5	MsOH	1	88
6	MeNO ₂ (0.05)	RT	1.5	MsOH	1	11
7	DCE (0.01)	0	1.5	MsOH	0.5	0
8	DCE (0.01)	0	1.5	MsOH	1.5	0
9	DCE (0.01)	40	1.5	MsOH	0.5	0
10	DCE (0.01)	40	1.5	MsOH	1.5	25
11	DCE (0.1)	0	1.5	MsOH	0.5	99 (88) ^b
12	DCE (0.1)	0	1.5	MsOH	1.5	61
13	DCE (0.1)	40	1.5	MsOH	0.5	84
14	DCE (0.1)	40	1.5	MsOH	1.5	8

^a Determined with ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^b Isolated yield. O/N = overnight.



Scheme 3 Reaction conditions and isolated yields for DDQ/H⁺ mediated homocoupling of benzofurans and benzothiofurans **1a–h** to **2a–h**. Substrates **1i** and **1j** failed to yield a product (see the text for details).

would be directly related to its reactivity. Consequently, we measured the relative oxidation potentials of compounds **1a–j** vs. FcH/FcH⁺ couple, and compared the results with data from theoretical calculations (Table 2). It is clearly evident that both oxidation potentials normalized to **1c** have strong systematic correlation (the absolute value is underestimated by ca. 0.31 V).²³ Furthermore, both the calculated and the experi-

Table 2 Experimental and calculated oxidation potentials (vs. FcH/FcH⁺)²²

Substrate	Exp. ^a (Exp.n.) ^b /V	Calc. (Calc.n.) ^b /V	Exp. – Calc. (Exp.n. – Calc.n.) ^b /V
1a	1.070 (0.280)	0.749 (0.305)	0.321 (–0.03)
1b	0.925 (0.135)	0.627 (0.183)	0.298 (–0.05)
1c	0.790 (0.000)	0.444 (0.000)	0.346 (0.00)
1d	0.810 (0.020)	0.557 (0.113)	0.253 (–0.09)
1e	1.055 (0.265)	0.782 (0.338)	0.273 (–0.07)
1f	1.000 (0.210)	0.689 (0.245)	0.311 (–0.04)
1g	0.845 (0.055)	0.527 (0.083)	0.318 (–0.03)
1h	0.910 (0.120)	0.595 (0.151)	0.315 (–0.03)
1i	1.310 (0.520)	1.060 (0.616)	0.250 (–0.10)
1j	1.100 (0.310)	0.685 (0.241)	0.415 (0.07)

^a Measurements were carried out in DCM with 0.05 M NBu₄PF₆ as the supporting electrolyte. ^b Values in parenthesis have been normalized to **1c** to see relative potentials.

mental oxidation potentials correlate well with the observed reactivity and provide a rationale as for why the homocoupling of **1i** was unsuccessful. With an oxidation potential of 1.310 V, **1i** is not oxidized by DDQ.

The oxidation potentials do not, however, explain why **1j** fails to homocouple even though it has an oxidation potential comparable to **1a** and **1f**. If we consider that dimerization involves the energetically closest MOs,²⁴ we can then pay our attention to the morphology of the SOMO of the radical cation and the HOMO of the neutral substrate. For a successful 3,3'-homocoupling, a high contribution from the C3-carbon to the nucleophile's HOMO and the electrophile's SOMO is imperative. As shown in Fig. 1, this is certainly true for **1a** but not for **1j**. Thus, it is clear that, in order to predict reactivity, both



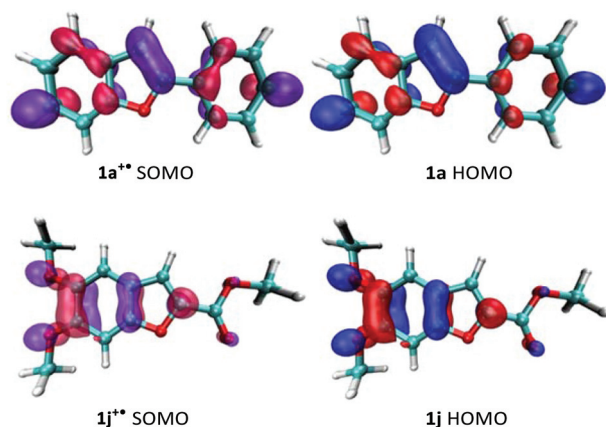
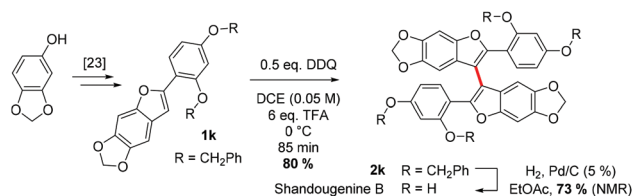


Fig. 1 Frontier molecular orbitals of **1a** and **1j** (HOMOs) and the respective cation radicals (SOMOs).

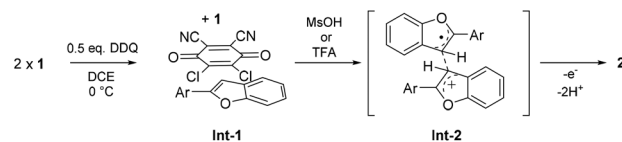
the oxidation potential of the substrate and the morphology of its frontier orbitals need to be considered.

Finally, to demonstrate the applicability of our approach, we endeavoured to synthesise shandougenine B. Prior to the synthesis, we predicted the oxidative homocoupling to be favourable based on its low oxidation potential and a high contribution from the C3-carbon to the frontier MOs (see the ESI†). Substrate **1k** was prepared with the reported literature procedure²⁵ and the homocoupling reaction promoted with 6 eq. of TFA and 0.5 eq. of DDQ (Scheme 4). To our delight, the dimerization of **1k** proceeded smoothly and the corresponding dimer could be isolated in 80% yield. After subsequent removal of the benzyl groups, the antioxidant shandougenine B was obtained in 73% yield (NMR) under standard conditions. Interestingly, the biological origin of shandougenine B has been hypothesised to be oxidative coupling of the monomer *Sophora* as it is also present in the roots of *Sophora tonkinensis*.^{14b} Our successful synthesis of shandougenine B *via* an oxidative route certainly supports this hypothesis.

In the proposed mechanism (Scheme 5), DDQ initially forms a charge transfer (CT) complex with the substrate (**Int-1**). The formation of a CT complex is seen visually by a colour change and confirmed by UV-vis spectroscopy for **1a–c** (Fig. 2 top). Furthermore, the structure of a 2 : 1 complex of **1c** and DDQ was determined by single crystal X-ray diffraction (Fig. 2 bottom, see the ESI† for details).²⁶ The layered structure



Scheme 4 Synthesis of shandougenine B with DDQ-mediated oxidative homocoupling as the key strategic step.



Scheme 5 Proposed reaction mechanism for the intermolecular oxidative dehydrogenative 3,3'-coupling of 2-aryl-benzo[*b*]furans and 2-aryl-benzo[*b*]thiophenes.

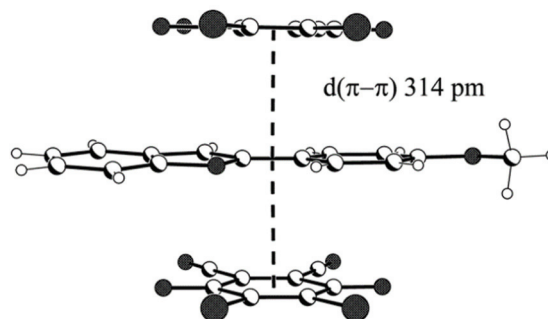
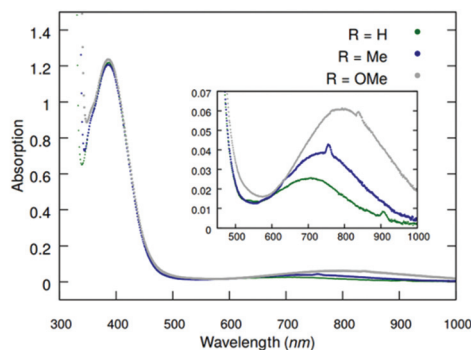


Fig. 2 (Top) UV-vis spectra of DCE solutions of **1a–c** and DDQ in a 2 : 1 ratio. (Bottom) Side view of the stacked packing of DDQ and **1c** in the crystal structure of a 1 : 2 adduct between DDQ and **1c**.

of the complex between **1c** and DDQ shows a short (3.14 Å) distance between the electron donor and the acceptor, which is a prerequisite for efficient electron transfer.²⁷

In our mechanistic scenario, the actual coupling reaction is initiated by a SET from **1** to DDQ, which is, in turn, triggered and promoted by addition of an acid that increases the oxidative power of DDQ.⁶ The formed electrophilic radical cation **1**^{•+} can then react with a nucleophilic neutral substrate **1** to form a radical cation intermediate **Int-2**, from which product **2** is obtained after elimination of two protons and a second SET. Alternatively, **1**^{•+} could deprotonate and couple with neutral **1** to form a neutral radical intermediate, leading to **2** *via* elimination of one proton and a second SET. At this point, the radical cation mechanism seems more likely as it is analogous to the one reported for MoCl₅-mediated dehydrogenative coupling of arenes.²⁸ Monitoring the reaction with NMR and EPR spectroscopy implies that the purported mechanism is conceivable as the disappearance of the NMR signals is accompanied by an appearance of an EPR signal upon

addition of the acid (see the ESI†). Moreover, our preliminary calculations show that the **Int-2** structure is a local minimum on the potential energy surface when **1**⁺ and **1** are coupled together *via* their C3-carbon atoms (see the ESI†). Detailed computational investigations of the reaction mechanism are currently underway.

Conclusions

We have developed a metal free DDQ/H⁺ mediated 3,3'-homocoupling reaction of 2-aryl-benzo[*b*]furans and 2-aryl-benzo[*b*]thiophenes. The feasibility of the reaction was found to correlate with the oxidation potential of the substrate and the morphology of its frontier molecular orbitals. The usefulness of this approach was demonstrated in *a priori* examination of the monomer Sophora that was successfully dimerized with the developed synthetic method, resulting in the first total synthesis of a natural product shandougenine B.

Experimental

Computational methods

All calculations were performed with the Turbomole 7.0 program package.²⁹ The solvent environment was taken into account with the COSMO approach with a dielectric constant of 10.125 for 1,2-dichloroethane.³⁰ The geometries were optimized using the TPSS functional³¹ augmented with D3 dispersion correction.³² Ahlrichs' def2-TZVP basis sets were used for all atoms as implemented in Turbomole.³³ A modified integration grid M4 was employed along with the MARI-J approximation augmented with a suitable auxiliary basis set.^{34,35} Vibrational frequencies were calculated numerically for all stationary points and were found to verify their correspondence to true minima (zero imaginary frequencies) and to obtain Gibbs free energies. Absolute oxidation potentials were calculated using a standard protocol ($E^{\circ} = \Delta G_{298.15} / nF$; where $n = 1$ and $F = 96.48 \text{ kcal mol}^{-1} \text{ V}^{-1}$) and were further normalized to the FcH/FcH⁺ couple in DCE by subtracting 4.927 eV from all calculated values.²³ The use of FcH/FcH⁺ couple as a reference for data employing nonaqueous solvents is recommended by IUPAC.³⁶ Molecular orbitals were visualized with the program VMD.^{24b}

General remarks

Unless otherwise specified, all materials were purchased from commercial sources and used as received without further purification. Known benzo[*b*]thiophenes were prepared with CuI/TMEDA catalysed annulation of 2-bromo alkynylbenzenes.³⁷ Known benzo[*b*]furans were synthesized from 2-iodophenol in a cascade Sonogashira/5-*endo*-dig cyclisation reaction similar to that described in the literature.³⁸

¹H, and ¹³C{¹H} NMR spectra were recorded using a Varian Mercury 300 or Varian Inova 500 spectrometer at 27 °C. ¹H spectra were referenced to tetramethylsilane (TMS, 0.0 ppm) or

to residual solvent peaks (CDCl₃ 7.26 ppm; *d*₆-DMSO 2.50 ppm, CD₃OD 3.31 ppm and CD₂Cl₂ 5.32 ppm). ¹³C{¹H} NMR spectra were referenced to residual solvent peaks (CDCl₃ 77.16 ppm; *d*₆-DMSO 39.52 ppm and CD₃OD 49.00 ppm). HRMS data were acquired with a JEOL JMS-700 instrument using EI ionization mode. UV-vis spectra were recorded on a Varian Cary 50 spectrometer at 27 °C. Cyclic voltammetry was performed with a Gamry Reference 600 potentiostat using a scan rate of 150 mV s⁻¹. Solid samples of **1a-j** (1–2 mg) were dissolved into a DCM solution containing 0.05 M of NBu₄PF₆ as the supporting electrolyte. Potentials were scanned at RT in a single compartment cell fitted with Pt electrodes and referenced to FcH/FcH⁺ couple. Details of single crystal X-ray structure determinations are given in the ESI.†

General procedure for homocouplings

Starting material (1 eq.) and DDQ (0.5 eq.) were mixed and dissolved in DCE (0.05 or 0.1 M). The formation of a CT-complex was observed from a colour change and the mixture was cooled to 0 °C and MsOH or TFA (3 or 6 eq.) was added to the mixture. After a given amount of time, the reaction mixture was filtered through a pad of basic Al₂O₃ and washed with chloroform. Purification of the crude product after evaporation of solvents was performed by flash chromatography (SiO₂).

2,2'-Bis(phenyl)-3,3'-bibenzo[*b*]furan (2a). Following the general procedure with 51.2 mg (0.264 mmol, 1 eq.) of **1a**, 30 mg (0.132 mmol, 0.5 eq.) of DDQ, 2.6 mL of DCE and 76.1 mg (0.792 mmol, 3 eq., 51 µl) of MsOH. Purification of the crude product with 0 : 1 → 40 : 1 (hexanes : EtOAc) afforded **2a** in 88% yield (44.7 mg, 0.116 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 7.9 Hz, 4H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26–7.21 (m, 6H), 7.16–7.08 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 154.5, 152.1, 130.6, 129.6, 128.7, 128.7, 126.4, 125.1, 123.2, 120.9, 111.4, 107.8.

2,2'-Bis(4-methylphenyl)-3,3'-bibenzo[*b*]furan (2b). Following the general procedure with 41.3 mg (0.198 mmol, 1 eq.) of **1b**, 22.5 mg (0.0992 mmol, 0.5 eq.) of DDQ, 2.0 mL of DCE and 57.2 mg (0.595 mmol, 3 eq., 38.6 µl) of MsOH. Purification of the crude product with 0 : 1 → 40 : 1 (hexanes : EtOAc) afforded **2b** in 92% yield (37.9 mg, 0.0914 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, *J* = 8.2 Hz, 4H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.35–7.30 (m, 2H), 7.16–7.09 (m, 4H), 7.07 (d, *J* = 8.2 Hz, 4H), 2.30 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 152.4, 138.7, 129.8, 129.4, 127.9, 126.3, 124.8, 123.1, 120.7, 111.2, 107.2, 21.5.

2,2'-Bis(4-methoxyphenyl)-3,3'-bibenzo[*b*]furan (2c). Following the general procedure with 43.9 mg (0.196 mmol, 1 eq.) of **1c**, 22.2 mg (0.0979 mmol, 0.5 eq.) of DDQ, 2.0 mL of DCE and 56.5 mg (0.587 mmol, 3 eq., 38 µl) of MsOH. Purification of the crude product with 20 : 1 (hexanes : EtOAc) afforded **2c** in 92% yield (40.1 mg, 0.0898 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) 7.76–7.71 (m, 4H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.34–7.29 (m, 2H), 7.16–7.09 (m, 4H), 6.82–6.77 (m, 4H), 3.75 (s, 6H). ¹³C NMR



(126 MHz, CDCl₃) δ 159.9, 154.3, 152.3, 129.9, 127.9, 124.5, 123.4, 123.0, 120.6, 114.2, 111.1, 106.2, 55.3.

***N,N'*-(3,3'-Bibenzo[*b*]furan)-2,2'-diylbis(1,4-phenylene)diacetamide (2d).** Following the general procedure under dry conditions with 14.3 mg (0.0569 mmol, 1 eq.) of **1d**, 6.6 mg (0.0291 mmol, 0.5 eq.) of DDQ, 1.14 mL of DCE and 32.8 mg (0.34 mmol, 6 eq., 22.2 μ l) of MsOH. Purification of the crude product with 20 : 1 (DCM : MeOH) afforded **2d** in 68% yield (9.7 mg, 0.0194 mmol). ¹H NMR (500 MHz, DMSO) δ 10.03 (s, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 4H), 7.53 (d, *J* = 8.7 Hz, 4H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 2H), 2.01 (s, 6H). ¹³C NMR (126 MHz, DMSO) δ 168.5, 153.6, 151.5, 139.9, 128.8, 126.4, 125.0, 124.2, 123.3, 119.9, 118.9, 111.4, 105.9, 24.0. HRMS (EI⁺) calcd for [C₃₂H₂₄N₂O₄]⁺ *m/z*: 500.1736, found: 500.1731.

2,2'-Bis(phenyl)-3,3'-bibenzo[*b*]thiophene (2e). Following the general procedure with 30.4 mg (0.145 mmol, 1 eq.) of **1e**, 16.4 mg (0.0723 mmol, 0.5 eq.) of DDQ, 1.4 mL of DCE and 41.7 mg (0.434 mmol, 3 eq., 28.2 μ l) of MsOH. Purification of the crude product with 0 : 1 \rightarrow 40 : 1 (hexanes : EtOAc) afforded **2e** in 86% yield (26.1 mg, 0.0624 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.39–7.32 (m, 4H), 7.27–7.22 (m, 2H), 7.12–7.08 (m, 2H), 7.07–7.01 (m, 8H). ¹³C NMR (75 MHz, CDCl₃) δ 142.5, 140.8, 139.0, 134.2, 128.5, 128.4, 127.8, 126.6, 124.8, 124.7, 123.8, 122.3.

2,2'-Bis(4-methylphenyl)-3,3'-bibenzo[*b*]thiophene (2f). Following the general procedure with 40.6 mg (0.181 mmol, 1 eq.) of **1f**, 20.5 mg (0.0905 mmol, 0.5 eq.) of DDQ, 1.8 mL of DCE and 52.2 mg (0.543 mmol, 3 eq., 35.3 μ l) of MsOH. Purification of the crude product with 0 : 1 (hexanes) \rightarrow 40 : 1 (hexanes : DCM) \rightarrow 20 : 1 (hexanes : EtOAc) \rightarrow 10 : 1 (hexanes : EtOAc) \rightarrow 1 : 1 (hexanes : EtOAc) afforded **2f** in 86% yield (26.1 mg, 0.0624 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) δ 7.90–7.87 (m, 2H), 7.35–7.29 (m, 4H), 7.24–7.19 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 4H), 6.93–6.89 (m, 4H), 2.24 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 142.4, 141.0, 138.7, 137.8, 131.4, 129.2, 128.2, 126.2, 124.6, 123.6, 122.2, 21.3.

2,2'-Bis(4-methoxyphenyl)-3,3'-bibenzo[*b*]thiophene (2g). Following the general procedure with 45.9 mg (0.191 mmol, 1 eq.) of **1g**, 21.7 mg (0.0955 mmol, 0.5 eq.) of DDQ, 3.8 mL of DCE and 55.1 mg (0.573 mmol, 3 eq., 37.2 μ l) of MsOH. Purification of the crude product with 20 : 1 (hexanes : EtOAc) \rightarrow 10 : 1 (hexanes : EtOAc) afforded **2g** in 93% yield (44.3 mg, 0.0884 mmol). Spectral data is in accordance with published data.^{18b} ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.36–7.28 (m, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 4H), 6.64 (d, *J* = 8.8 Hz, 4H), 3.71 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 159.4, 142.2, 141.0, 138.6, 129.6, 126.8, 125.7, 124.6, 124.5, 123.5, 122.2, 113.9, 55.3.

2,2'-Bis(2-thienyl)-3,3'-bibenzo[*b*]thiophene (2h). Following the general procedure with 36.5 mg (0.169 mmol, 1 eq.) of **1h**, 19.1 mg (0.0844 mmol, 0.5 eq.) of DDQ, 1.7 mL of DCE and 48.7 mg (0.5061 mmol, 3 eq., 32.9 μ l) of MsOH. Purification of the crude product with 0 : 1 \rightarrow 40 : 1 afforded **2h** in 15% yield

(5.2 mg, 0.01237 mmol). ¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.38–7.30 (m, 2H), 7.22–7.18 (m, 6H), 7.07 (d, *J* = 5.0 Hz, 2H), 6.86 (t, *J* = 4.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 140.7, 138.3, 137.2, 135.9, 127.5, 127.1, 126.5, 125.3, 125.1, 123.2, 122.2, 77.2. HRMS (EI⁺) calcd for [C₂₄H₁₄S₄]⁺ *m/z*: 429.9978, found: 429.9984

Benzylated shandougenine B (2k)

Following the general procedure under dry conditions and under Ar with 16.1 mg (0.0357 mmol, 1 eq.) of **1k**, 4.1 mg (0.0179 mmol, 0.5 eq.) of DDQ, 0.72 mL of DCE and 24.4 mg (0.214 mmol, 6 eq., 16.5 μ l) of TFA. Purification of the crude product with 20 : 1 \rightarrow 5 : 1 \rightarrow 3 : 1 (hexanes : EtOAc) afforded **2k** in 80% yield (12.9 mg, 0.01435 mmol). ¹H NMR (300 MHz, CDCl₃) δ 7.42–7.31 (m, 10H), 7.23–7.16 (m, 6H), 7.09–7.03 (m, 4H), 7.01–7.00 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.67–6.66 (m, 2H), 6.31 (d, *J* = 2.3 Hz, 2H), 6.26 (dd, *J* = 8.5, 2.3 Hz, 2H), 5.96 (dd, *J* = 5.1, 1.3 Hz, 4H), 4.91 (s, 4H), 4.61 (s, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 160.2, 157.4, 150.3, 149.8, 145.9, 144.2, 136.9, 131.6, 128.8, 128.3, 128.2, 127.6, 126.9, 122.8, 113.9, 110.4, 105.9, 101.2, 100.9, 99.4, 93.3, 70.2, 69.9.

Shandougenine B

2k (6.5 mg, 0.00723 mmol) and 25 mg of 5% Pd/C (wetted ~50% H₂O) in 2.5 mL ethyl acetate were stirred vigorously for 10 h 30 min under a H₂-balloon. After filtration through diatomaceous earth, evaporation of volatiles and redissolution to CD₃OD, shandougenine B was obtained in 73% yield (NMR). The analytical sample was purified with column chromatography using 10 : 1 (DCM : MeOH) as the eluent. Spectral data is in accordance with published data.^{14b} ¹H NMR (500 MHz, CD₃OD) δ 7.40 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 2H), 6.40 (dd, *J* = 8.5, 2.4 Hz, 2H), 6.27 (s, 2H), 6.19 (d, *J* = 2.3 Hz, 2H), 5.85 (d, *J* = 7.2 Hz, 4H). ¹³C NMR (75 MHz, CD₃OD) δ 160.8, 157.0, 151.5, 151.1, 147.2, 145.5, 131.8, 123.5, 111.6, 110.7, 108.8, 103.7, 102.4, 99.8, 93.9. HRMS (EI⁺) calcd for [C₃₀H₁₈O₁₀]⁺ *m/z*: 538.0900 found: 538.0899.

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