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Evidence of single electron transfer from the enolate anion of an *N,N'*-dialkyldiketopiperazine additive in BHAS coupling reactions

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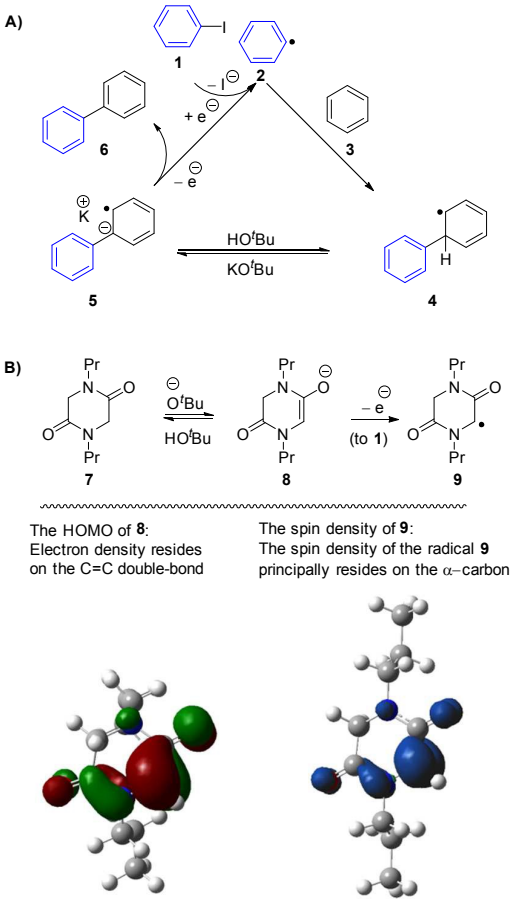
Abstract. A designed *N,N'*-dialkyldiketopiperazine (DKP) provides evidence for the role of DKP additives as initiators that act by electron transfer in base-induced homolytic aromatic substitution reactions, involving coupling of haloarenes to arenes.

Introduction

There has been an explosion of interest in transition metal-free reactions, used to achieve aryl-aryl bond formations between a haloarene and an arene.[1-15] The mechanism is believed to follow the base-promoted homolytic aromatic substitution pathway (BHAS) (Scheme 1A).[16] The initiation step involves a single electron transfer (SET) to the haloarene to form the aryl radical **2**, and this aryl radical attacks a molecule of arene, e.g. benzene **3,** to form the inter-ring bond in **4**. Radical **4** undergoes a deprotonation to yield radical anion **5**, which is electron-rich and donates an electron to the starting material **1** to form the product **6** and propagate the radical chain. Although it is accepted that the initiation step is a SET process, the species responsible for this initial electron donation to **1** has been debated. Recent findings point to the formation of an organic electron donor that is created by the reaction between KO^{t}Bu and an organic additive.[17-19] One of the most successful additives is the *N,N'*-dipropyldiketo-piperazine (DKP) additive **7**, which was very effective in promoting C-C bond formation both in transition metal-free aryl-aryl couplings and in $S_{RN}1$ reactions.[18,20,21] It has been proposed that the DKP additive **7**, in the presence of KO^{t}Bu, forms an electron-rich enolate anion **8**, which donates an electron to the haloarene **1** in the initiation step of the BHAS reaction pathway and, in doing so, forms the captodatively stabilised radical **9** (Scheme 1B).[18] The aim of this project was to look for evidence that the enolate anion of DKP **8** donates an electron to the haloarene, such as **1**, to form the captodative radical **9**, under the transition metal-free reaction conditions.

The first step in achieving this goal was to design and prepare an analogue of the DKP additive, **7,** that is capable of trapping a captodatively stabilised radical like **9**, and therefore reporting that SET can take place from DKP additives under the conditions of the coupling reactions. Radicals analogous to **9**



Scheme 1A) The base-promoted homolytic aromatic substitution mechanism.[16] **B**) The proposed electron donor **8** formed *in situ* from DKP **7.**

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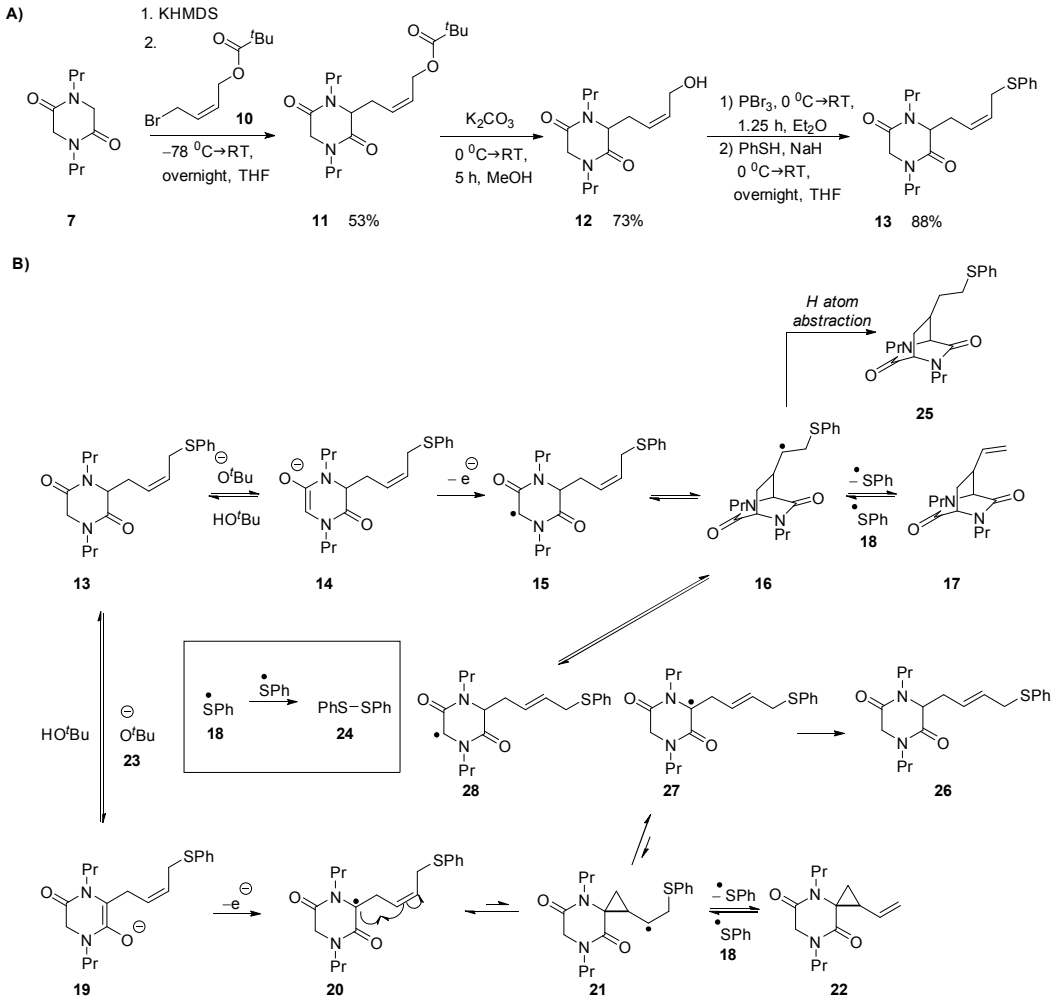

Scheme 2.A) Synthesis of the additive **13** from **7**. **B**) The mechanism of cyclisation of **15** and **20**, both of which arise through SET from an enolate anion of DKP additive **13**.

can be trapped intramolecularly by an appropriate tether on the DKP scaffold.[23-25] For example, Jahn *et al*. synthesised diketopiperazines that contained alkene "tethers" attached to the DKP scaffold. They prepared TEMPO-derivatives as precursors to radicals analogous to **9**. Homolysis of these derivatives liberated the radicals which successfully cyclised onto the alkene within the tether to form bridged diketopiperazine products. Based on this information, allylic sulfide **13** was identified as our candidate probe. Its synthesis is shown in Scheme 2A. Deprotonation of **7** and allylation with bromide **10** afforded **11** (53%). Hydrolysis of the pivalate ester and conversion of the resulting alcohol (73%) into the bromide was followed by displacement by the thiolate to yield **13** (88% over two steps).

The initial investigations were to determine whether its derived enolate anions, **14** and/or **19**, (Scheme 2B) were capable of donating an electron, and, if so, what products would be observed from the radicals formed, **15** and **20**, through cyclisation onto the *cis*-alkene within the tether, under the conditions of the BHAS coupling reaction. The cyclised radicals could progress as shown in Scheme 2B;

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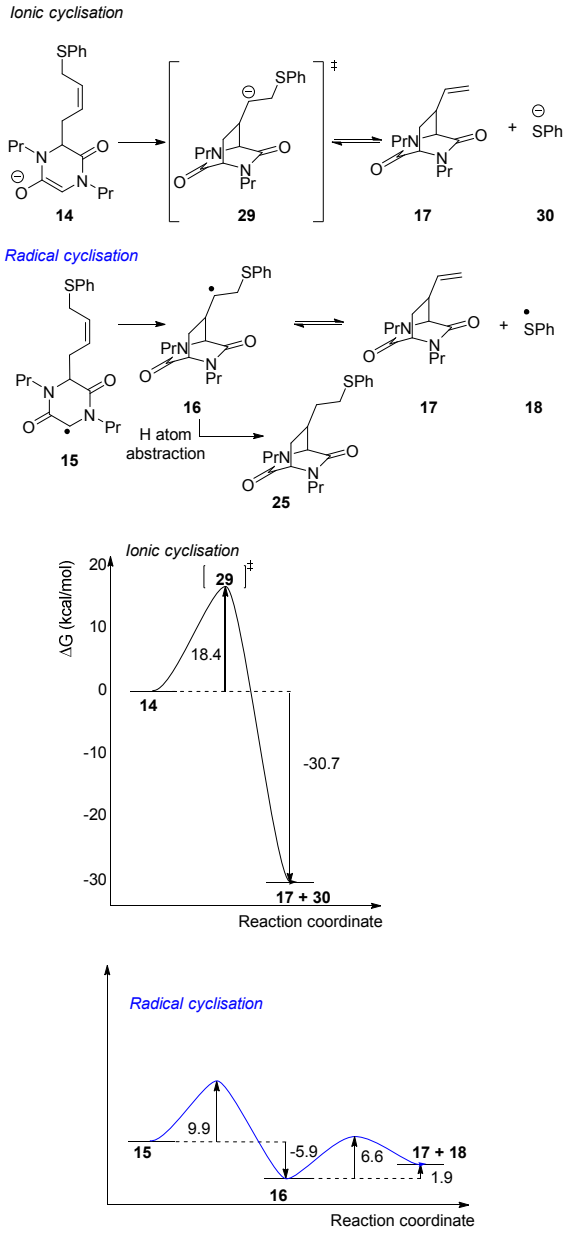
Looking firstly at radical **20**, the equilibria between cyclopropylcarbinyl radical **21** and captodative radicals **20** and **27** is likely to lie heavily in favour of the captodative radicals, [notably the more stable (*E*)-isomer **27**] due not only to their stabilisation, but also to the added strain present in the cyclopropane in **21**. This means that radical **21** is unlikely to proceed to vinylcyclopropane **22**. The most likely outcome is that radical **27** is converted to closed-shell diketopiperazine **26** by hydrogen atom abstraction (*e.g*. from another molecule of **13**).

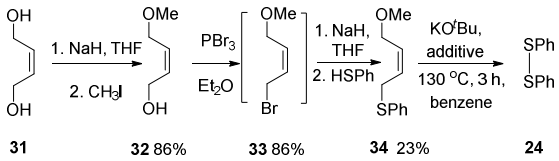


Scheme 3. Ionic (black line) *vs*. radical cyclisation (blue line) and cleavage of the C-S bond, in benzene as solvent.

On the other hand, cyclisation of **15** affords radical **16**, for which three types of termination could occur: (i) loss of phenylthiyl radical **18** would afford alkene **17**; (ii) hydrogen atom abstraction, likely from another molecule of **13**, would convert **16** to **25**; (iii) reversal of the ring-closure would afford **15** or, more likely, its (*E*)-isomer **28**. Detection of the (*E*)-isomer of **13** at the end of the reaction could therefore support a pathway involving reversible radical cyclisation.

Radical cyclisation to give bridged products is possible, but we were curious to compare the energy landscape for anionic cyclisation from the enolate with the radical pathway, and so computational analysis of the two possibilities was performed (Scheme 3). *In silico*, the anionic cyclisation of enolate **14** formed **17** in a concerted mechanism. However, the cyclisation *via* the radical pathway shows that the intermediate **16** is the most stable species in the reaction pathway. The equilibrium for the thiyl radical elimination from **16** was computationally modelled and the C-S fragmentation to form **17** and **18** was calculated to be endergonic: $\Delta G^{\ddagger}$ = 6.6 kcal/mol and ΔG_{rxn} = 1.9 kcal/mol. This agrees with previously reported equilibria for elimination of thiyl radicals in the formation of alkenes.[25] From **16**, hydrogen atom abstraction leads to **25**, so **25** is a signature product from a radical cyclisation process.

Table 1. The synthesis of allylic thioether **34** and its reactions with KO^{t}Bu, in the presence of various additives



Entry	**Additive** (eq.)	KO^t**Bu** (eq.)	**24**[a.] (%)
1	--	1	0[b.]
2	DKP **7** (1)	2	6[b.]
3	**35** (1) (pinacolone)	2	4[b.]

[a.] *Isolated yield.* [b.] *Yield calculated using 1,3,5-trimethoxybenzene as the internal standard in* ^{1}*H-NMR of the crude mixture. (spectra were compared with an authentic and pure samples).*

We were also keen to probe anionic chemistry experimentally to investigate the effect of basic conditions on an allylic thioether. The substrate **34**, which is analogous to the tether on the additive **12**, was synthesised and reacted under the different reaction conditions to determine (i) whether diphenyl disulfide is formed (in the absence of radical conditions, it was expected not to form) and (ii) to check whether isomerisation of the (*Z*)-alkene occurred under the basic conditions (Table 1). When the substrate **34** was reacted in the presence of KO^{t}Bu, no diphenyl disulfide **24** was observed in the crude reaction mixture (Table 1, entry 1; note that no **34** was recovered).

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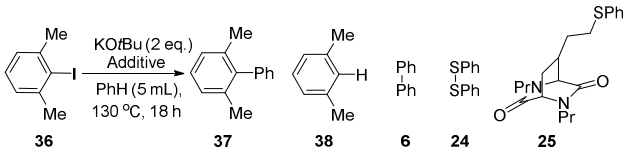
However, when either the DKP additive **7** (Table 1, entry 2) or pinacolone **35,** ^{t}Bu(C=O)Me (Table 1, entry 3) was used in the presence of KO^{t}Bu, diphenyl disulfide **24** was formed (6% and 4% respectively). In these cases, both DKP **7** and pinacolone **35** are transformed into their respective enolate anions under the basic conditions of the reaction; and pinacolone enolate has previously been shown to act as an electron donor to haloarenes to initiate $S_{RN}1$ reactions in DMSO.[26,27]

The additive **13** was now applied to the transition metal-free reaction conditions used in the coupling of iodoarenes to benzene. The iodo-*m*-xylene **36** substrate was used to assess whether an electron donor is formed from the DKP additive, because in the transition metal-free coupling reactions the substrate **36** is activated towards coupling exclusively through a SET initiation step (Table 2).[18]

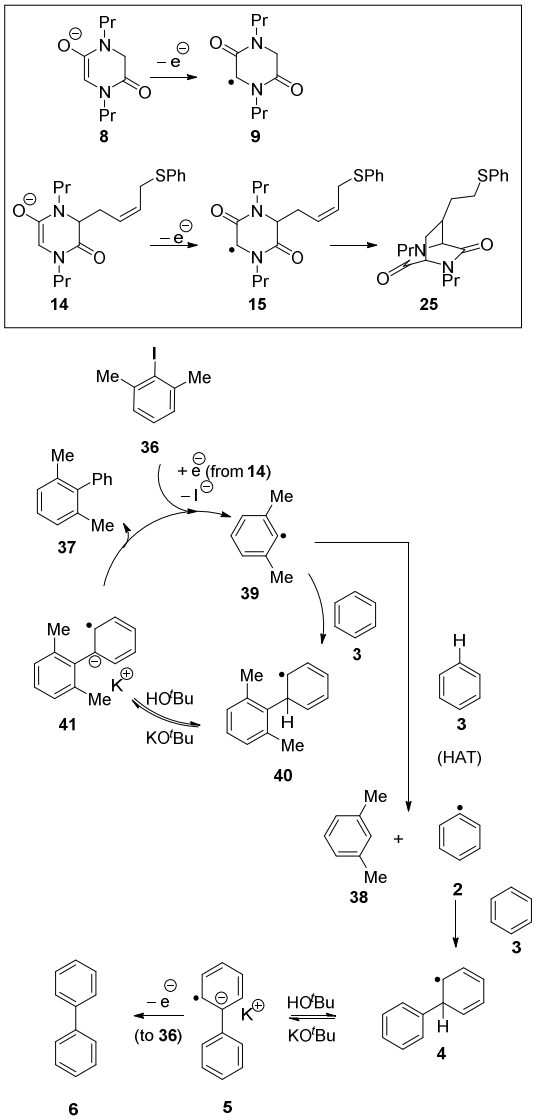
Table 2. Aryl-aryl bond formation between iodo-*m*-xylene **36** and benzene using various additives.



Entry	Additive (eq.)	36 (%)	37 (%)	38 (%)	6 (%)	24 (%)	25 (%)
1	--	98[a.]	--	--	--	--	--
2	**7** (0.2)	16[a.]	6[a.]	3[a.]	26[a.]	--	--
3	**13** (0.2)	53[a]	4[a.]	10[a.]	13[a.]	28[a,b] (27)[c]	20[a,b] (14)[c]

[a]*Yield calculated using 1,3,5-trimethoxybenzene as the internal standard in* ^{1}*H-NMR of the crude mixture.* [b]*Yield calculated using the DKP additive* ***13*** *as the limiting reagent.* [c]Isolated yield.

Three reactions were performed, under inert atmosphere, to determine how efficiently the additive **13** can promote the coupling between the iodo-*m*-xylene **36** and benzene: (i) The first reaction exposed iodo-*m*-xylene **36** to KO^{t}Bu in the absence of any organic additive (Table 2, entry 1) and after 18 h at 130 °C, 98% of the starting material **36** remained unreacted. (ii) Next, the iodo-*m*-xylene **36** was treated with KO^{t}Bu and sub-stoichiometric amounts of additive **7** under the same reaction conditions. This reaction gave much higher conversion of the iodo-*m*-xylene **36** (only 16% remained unreacted), and the rest of the products formed were **37** (6%), volatile *m*-xylene **38** (3%) and biphenyl **6** (26%) (Table 2, entry 2). The ratio of yields of **37** to **6** (approximately 1: 4) was characteristic of previous BHAS experiments performed in these transition metal-free reaction conditions.[17-19,28] (iii) The final reaction was to expose **36** to KO^{t}Bu and sub-stoichiometric amounts of additive **13** (Table 2, entry 3) whereupon the compounds obtained were: unreacted starting material **36** (53%), **37** (4%), **38** (10%), **6** (13%), **24** (28%) and **25** (20%).



Scheme 4. A modification of the BHAS pathway for the reaction of substrate iodo-*m*-xylene **36**.[18]

To couple iodo-*m*-xylene **36** with benzene through the BHAS reaction pathway, an additive, either **7** or **13**, is required in the reaction because the reaction of **36** with KO^{t}Bu and no additive returned only starting material (Table 2, entry 1). Iodo-*m*-xylene – **36** in the presence of KO^{t}Bu and either **7** or **13** (Table 2, entries 2–3) formed products **37**, **38** and **6,** which are known products for the reaction of iodo-*m*-xylene **36** *via* the BHAS pathway, thus providing evidence that the additive **13** is capable of promoting the transition metal-free aryl-aryl bond formation, similarly to DKP **7**.[18] SET to **36** (Scheme 4) leads to cleavage of the C-I bond with the formation of the aryl radical **39** and loss of an iodide anion. The aryl radical **39** can react in two ways: (i) it attacks a molecule of benzene to ultimately form product **37** through the BHAS pathway. (ii) The aryl radical **39** abstracts a hydrogen atom from a molecule of benzene to form xylene **38** and the aryl radical **2**. The aryl radical **2** will

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undergo the BHAS mechanism and ultimately leads to radical anion **5**. Finally, this converts to biphenyl product **6** through transfer of an electron to substrate **36**, which propagates the chain reaction.The formation of the product **25** supports the formation of the captodatively stabilised radical **15** in the reaction conditions. The formation of the radical **15** (or **9**) occurs through a SET from the enolate anion of the additive **14** (or **8**), which provides evidence that the enolate anion donates a single electron to iodo-*m*-xylene **36** to initiate the transition metal-free aryl-aryl bond formation. Comparison of the reactions performed using the two possible additives, **7** and **13**, suggests they both react through similar reaction pathways. This is supported with the computational analysis; SET from the enolate anion **8** (Scheme 4) to iodo-*m*-xylene **36** is possible under the reaction conditions, $\Delta G^{\ddagger}$ = 23.0 kcal/mol and ΔG_{rxn} = 10.3 kcal/mol, and SET from the enolate anion **14** to iodo-*m*-xylene **36** has the energy profile, $\Delta G^{\ddagger}$ = 25.0 kcal/mol and ΔG_{rxn} = 13.3 kcal/mol. Both these energy profiles for SET are accessible at 130 ^{o}C, however the enolate anion of the DKP additive **8** has a more favourable overall energy profile for SET, which suggests that the conversion of **36** into products would be more efficient using the DKP additive **7** rather than additive **13**, which was borne out experimentally. These reactions simply provide initiation for the BHAS radical chain reaction, and it is likely that not many chains are needed to convert substrates to product.

Conclusions

This study has provided evidence that the additive **13** behaves analogously to **7**, and that the enolate anion of additive **13** donates an electron to haloarenes under these transition metal-free reaction conditions. Therefore, the role of the additive **7** in these transition metal-free reaction conditions, is to form the enolate anion *in situ* and this enolate anion **8** is the electron donor species that initiates the BHAS mechanism (Scheme 4). This supports the growing body of evidence relating to the role of organic electron donors in these reactions.

Experimental

General experimental information.

All reagents were bought from commercial suppliers and used without further purification unless stated otherwise. All the reactions were carried out under argon atmosphere. Diethyl ether, tetrahydrofuran, dichloromethane and hexane were dried with a Pure-Solv 400 solvent purification system by Innovative Technology Inc., U.S.A. Organic extracts were, in general, dried over anhydrous sodium sulphate (Na_2SO_4). A Büchi rotary evaporator was used to concentrate the reaction mixtures. Thin layer chromatography (TLC) was performed using aluminium-backed sheets of silica gel and visualised under a UV lamp (254 nm). The plates were developed using phosphomolybdic acid or KMnO4 solution. Column chromatography was performed to purify compounds by using silica gel 60 (200-400 mesh).

The electron transfer reactions were carried out within a glove box (Innovative Technology Inc., U.S.A.) under nitrogen atmosphere, and performed in oven-dried or flame-dried apparatus using anhydrous solvents, which were either degassed under reduced pressure, then purged with argon and dried over activated molecular sieves (3 Å), prior to being sealed and transferred to the glovebox. All solvents or samples introduced into the glovebox were transferred through the port, which was evacuated and purged with nitrogen ten times before entry. When the reaction mixtures were prepared, the reaction vessel was removed from the glovebox and the rest of the reaction was performed in a fumehood.

Proton (^{1}H) NMR spectra were recorded at 400.13, 400.03 and 500.16 MHz on Bruker AV3, AV400 and AV500 spectrometers, respectively. Carbon (^{13}C) NMR spectra were recorded using broadband decoupled mode at 100.61, 100.59 and 125.75 MHz on Bruker AV3, AV400 and AV500 spectrometers, respectively. Spectra were recorded in either deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (d_6-DMSO), depending on the solubility of the compounds. The chemical shifts are reported in parts per million (ppm) calibrated on the residual non-deuterated solvent signal, and the coupling constants, *J*, are reported in Hertz (Hz). The peak multiplicities are denoted using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; m, multiplet; br s, broad singlet; dd, doublet of doublets; dd, doublet of triplets; td, triplet of doublets.

Infra-Red spectra were recorded on an ATR-IR spectrometer. Melting points were determined on a Gallenkamp Melting point apparatus. The mass spectra were recorded by either gas-phase chromatography (GCMS) or liquid-phase chromatography (LCMS), using various ionisation techniques, as stated for each compound: atmospheric pressure chemical ionisation (APCI), electron ionisation (EI), electrospray ionisation (ESI). GCMS data were recorded using an Agilent Technologies 7890A GC system coupled to a 5975C inert XL EI/CI MSD detector. Separation was performed using the DB5MS-UI column (30 m x 0.25 mm x 0.25 µm) at a temperature of 320 ^{o}C, using helium as the carrier gas. LCMS data were recorded using an Agilent 6130 Dual source mass spectrometer with Agilent 1200, Agilent Poroshell 120 EC-C18 4.6mm x 75mm x 2.7µm column. High-resolution mass spectrometry (HRMS) was performed at the University of Wales, Swansea, in the EPSRC National Mass Spectrometry Centre. Accurate mass was obtained using atmospheric pressure chemical ionisation (APCI), chemical ionisation (CI), electron ionisation (EI), electrospray ionisation (ESI) or nanospray ionisation (NSI) with a LTQ Orbitrap XL mass spectrometer.

Synthesis of 1,4-dipropylpiperazine-2,5-dione 7.[27] Anhydrous dichloromethane (30 mL) was added to a round-bottomed flask. Under an argon atmosphere, at 0 ^{o}C, chloroacetyl chloride (4 mL, 50 mmol) and *n*-propylamine (8.6 mL, 105 mmol, 2.1 eq.) were simultaneously added dropwise. The reaction mixture was stirred at 0 ^{o}C for 15 min and then diluted with diethyl ether (200 mL) and a solid precipitated.

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The reaction mixture was filtered, and the solid was washed with diethyl ether. The filtered solution was concentrated *in vacuo* and diluted with diethyl ether (200 mL) and filtered a second time. The filtered solution was concentrated *in vacuo* to give 2-chloro-*N*-propylacetamide[28] (6.72 g, 99%) as a pale yellow oil [Found: (HRMS-ESI) 136.0521. $C_5H_{11}ClNO^+$ $(M+H)^+$ requires 136.0524]; ν_{max}(film) / cm^{-1} 3292, 3084, 2965, 2936, 2876, 1651, 1539, 1460, 1439, 1258, 1240, 1155; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 7.2 Hz, C*H*$_3$), 1.50 (2 H, sx, *J* = 7.2 Hz, C*H*$_2$), 3.18 – 3.23 (2 H, m, C*H*$_2$), 4.01 (2 H, s, C*H*$_2$), 6.67 (1 H, br s, N*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.4 (CH_3), 22.7 (CH_2), 41.6 (CH_2), 42.8 (CH_2), 165.9 (C). 2-Chloro-*N*-propylacetamide (6.78 g, 50 mmol) and anhydrous tetrahydrofuran (30 mL) were added to a flame-dried round-bottomed flask. At 0 °C, a suspension of sodium hydride (60% in mineral oil, 2.2 g, 55 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (20 mL) was added dropwise *via* cannula and the reaction mixture was stirred at RT for 3.5 h. The reaction mixture was quenched by dropwise addition of water and diluted with diethyl ether (150 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0 - 100% ethyl acetate in hexane) to give 1,4-dipropylpiperazine-2,5-dione **7**[29] (2.66 g, 54%) as pale yellow crystals m.p. 54 – 59 °C (lit:[29] 40 – 42 °C); [Found: (HRMS-ESI) 199.1438. $C_{10}H_{19}N_2O_2^+$ $(M+H)^+$ requires 199.1438]; ν_{max}(film) / cm^{-1} 2964, 2932, 2872, 1647, 1483, 1335, 1308, 1277, 1204, 1055; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.92 – 0.95 (6 H, m, 2 x C*H*$_3$), 1.59 (4 H, sx, *J* = 7.5 Hz, 2 x C*H*$_2$), 3.37 (4 H, m, 2 x C*H*$_2$), 3.96 (4 H, s, C*H*$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.2 (2 x CH_3), 20.0 (2 x CH_2), 47.7 (2 x CH_2), 50.0 (2 x CH_2), 163.6 (2 x C).

Synthesis of *cis*-4-bromobut-2-en-1-yl pivalate 10. Sodium hydride (60% in mineral oil, 1.1 g, 27.4 mmol, 1.0 eq.) and anhydrous tetrahydrofuran (120 mL) were added to a flame-dried round-bottomed flask. Under an argon atmosphere, at 0 °C, *cis*-2-butene-1,4-diol (2.3 mL, 27.4 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 10 min, then at RT for 45 min. Trimethylacetyl chloride (3.4 mL, 27.4 mmol, 1.0 eq.) was added dropwise *via* syringe pump over a period of 30 min and the reaction mixture was stirred at RT overnight and then quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0 – 20% ethyl acetate in hexane) to give *cis*-4-hydroxybut-2-en-1-yl pivalate[29] (4.70 g, 99%) as a pale yellow oil [Found: (HRMS-ESI) 173.1169. $C_9H_{17}O_3^+$ $(M+H)^+$ requires 173.1172]; ν_{max}(film) / cm^{-1} 3412, 2972, 2872, 1726, 1479, 1280, 1146, 1030, 983, 939, 858, 772; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (9 H, s, 3 x C*H*$_3$), 4.26 (2 H, d, *J* = 6.4 Hz, C*H*$_2$), 4.67 (2 H, d, *J* = 7.2 Hz, C*H*$_2$), 5.61 (1 H, dt, *J* = 11.2, 7.2 Hz, *cis*-C*H*), 5.85 (1 H, dt, *J* = 11.2, 6.4 Hz, *cis*-C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 27.3 (3 x CH_3), 38.9 (C), 58.6 (CH_2), 60.2 (CH_2), 126.0 (CH), 133.3 (CH), 178.9 (C).

Cis-4-hydroxybut-2-en-1-yl pivalate (3.05 g, 17.7 mmol) and anhydrous diethyl ether (10 mL) were added to a round-bottomed flask. Under an argon atmosphere, at 0 °C, PBr_3 (0. 7 mL, 7.1 mmol, 0.4 eq.) was added slowly and the reaction mixture was stirred at 0 °C for 45 min, then at RT overnight. The reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give *cis*-4-bromobut-2-en-1-yl pivalate **10** (4.01 g, 96%) as a colourless oil [Found: (HRMS-APCI) 235.0330. $C_9H_{16}{}^{79}BrO_2^+$ $(M+H)^+$ requires 235.0328]; ν_{max}(film) / cm^{-1} 2972, 1724, 1479, 1396, 1279, 1140, 1032, 966, 939, 769, 725; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (9 H, s, 3 x C*H*$_3$), 4.03 (2 H, d, *J* = 8.4 Hz, C*H*$_2$), 4.68 (2 H, d, *J* = 6.8 Hz, C*H*$_2$), 5.68 (1 H, dt, *J* = 10.8, 6.8 Hz, *cis*-C*H*), 5.93 (1 H, dt, *J* = 10.8, 8.4 Hz, *cis*-C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.0 (CH_2), 27.3 (3 x CH_3), 38.9 (C), 59.3 (CH_2), 128.6 (CH), 129.8 (CH), 178.4 (C); *m/z* (APCI) 237.0310 [$(M+H)^+$, ^{81}Br, 98%], 235.0330 [$(M+H)^+$, ^{79}Br, 100].

Synthesis of *cis*-4-(3,6-dioxo-1,4-dipropylpiperazin-2-yl)but-2-en-1-yl pivalate 11. 1,4-Dipropylpiperazine-2,5-dione **7** (2.57 g, 13.0 mmol) and anhydrous tetrahydrofuran (110 mL) were added to a flame-dried round-bottomed flask. Under an argon atmosphere, at −10 °C, a solution of KHMDS (2.91 g, 14.5 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (40 mL) was added slowly and the reaction mixture was stirred at −10 °C for 20 min, then at RT for 15 min. At −78 °C, *cis*-4-bromobut-2-en-1-yl pivalate **10** (3.67 g, 15.6 mmol, 1.2 eq.) was added slowly and the reaction mixture was stirred at −78 °C for 30 min, then at RT overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (a few drops) and the crude mixture was concentrated *in vacuo*. The crude mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 x 60 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0 - 20% ethyl acetate in hexane) to give *cis-4-(3,6-dioxo-1,4-dipropylpiperazin-2-yl)but-2-en-1-yl pivalate* ***11*** (2.40 g, 53%) as a yellow oil [Found: (HRMS-ESI) 375.2252. $C_{19}H_{32}N_2O_4Na^+$ $(M+Na)^+$ requires 375.2254]; ν_{max}(film) / cm^{-1} 2965, 2874, 1724, 1655, 1464, 1329, 1148, 1065, 1032, 953; ^{1}H-NMR (400 MHz, $CDCl_3$); δ 0.91 (6 H, t, *J* = 7.6 Hz, 2 x C*H*$_3$), 1.18 (9 H, s, 3 x C*H*$_3$), 1.50 – 1.67 (4 H, m, 2 x C*H*$_2$), 2.65 (1 H, dt, *J* = 14.8, 7.2 Hz, C*H*$_2$), 2.77 – 2.84 (2 H, m, 2 x C*H*$_2$), 3.15 – 3.22 (1 H, m, C*H*$_2$), 3.47 – 3.52 (1 H, m, C*H*$_2$), 3.78 (1 H, d, *J* = 17.6 Hz, C*H*$_2$), 3.89 – 4.09 (3 H, m, 2 x C*H*$_2$ and C*H*), 4.56 (2 H, d, *J* = 7.2 Hz, C*H*$_2$), 5.58 (1 H, dt, *J* = 11.2, 7.6 Hz, *cis*-C*H*), 5.70 (1 H, dt, *J* = 11.2, 6.8 Hz, *cis*-C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (CH_3), 11.4 (CH_3), 20.1 (CH_2), 20.6 (CH_2), 27.3 (3 x CH_3), 30.4 (CH_2), 38.9 (C), 46.2 (CH_2), 48.0 (CH_2), 50.0 (CH_2), 59.8 (CH_2), 60.1 (CH), 126.8 (CH), 129.3 (CH), 164.2 (C), 165.9 (C), 178.4 (C).

Synthesis of *cis*-3-(4-hydroxybut-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione 12. *Cis*-4-(3,6-dioxo-1,4-dipropylpiperazin-2-yl)but-2-en-1-yl pivalate **11** (2.37 g, 6.7 mmol) and methanol (40 mL) were added to a round-bottomed flask. Under an argon atmosphere, at 0 °C, K_2CO_3 (1.11 g, 8.0 mmol, 1.2 eq.) was added and the reaction mixture was stirred at RT for 3 h. The reaction was incomplete by TLC analysis. At 0 °C, K_2CO_3

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(463 mg, 3.35 mmol, 0.5 eq.) was added and the reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched with water (a few drops) and the crude mixture was concentrated *in vacuo*. The crude mixture was diluted with water (40 mL) and extracted with dichloromethane (4 x 40 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0→100% ethyl acetate in hexane) to give *cis-3-(4-hydroxybut-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione* ***12*** (1.33 g, 73%) as a pale yellow oil [Found: (HRMS-ESI) 291.1676. $C_{14}H_{24}N_2O_3Na^+$ $(M+Na)^+$ requires 291.1679]; ν_{max}(film) / cm^{-1} 3410, 2963, 2932, 2874, 1643, 1468, 1331, 1200, 1032, 718; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (6 H, t, *J* = 7.6 Hz, 2 x C*H*$_3$), 1.52 – 1.63 (4 H, m, 2 x C*H*$_2$), 2.54 – 2.75 (2 H, m, C*H*$_2$ and O*H*), 2.75 – 2.84 (2 H, m, C*H*$_2$), 3.15 – 3.22 (1 H, m, C*H*$_2$), 3.40 – 3.47 (1 H, m, C*H*$_2$), 3.78 (1 H, d, *J* = 17.6 Hz, C*H*$_2$), 3.87 – 3.94 (1 H, m, C*H*$_2$), 4.01 – 4.10 (4 H, m, 3 x C*H*$_2$ and the C*H*), 5.46 (1 H, dt, *J* = 10.8, 7.6 Hz, *cis*-C*H*), 5.81 (1 H, dt, *J* = 10.8, 6.8 Hz, *cis*-C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (CH_3), 11.3 (CH_3), 20.0 (CH_2), 20.5 (CH_2), 29.9 (CH_2), 46.2 (CH_2), 48.0 (CH_2), 49.9 (CH_2), 58.1 (CH_2), 60.2 (CH), 124.2 (CH), 134.6 (CH), 164.4 (C), 166.2 (C).

Synthesis of *cis*-3-(4-(phenylthio)but-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione 13. *Cis*-3-(4-hydroxybut-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione **12** (1.13 g, 4.2 mmol) and anhydrous diethyl ether (2 mL) were added to a round-bottomed flask. Under an argon atmosphere, at 0 °C, PBr_3 (0.16 mL, 1.7 mmol, 0.4 eq.) was added slowly and the reaction mixture was stirred at RT for 1 h 15 min. The reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (4 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give *cis-3-(4-bromobut-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione* (1.20 g, 86%) as a pale yellow oil [Found: (HRMS-ESI) 331.1018. $C_{14}H_{24}{}^{79}BrN_2O_2^+$ $(M+H)^+$ requires 331.1016]; ν_{max}(film) / cm^{-1} 2963, 2932, 2874, 1655, 1466, 1327, 1202, 1155, 1063, 893, 743; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (6 H, t, *J* = 7.6 Hz, 2 x C*H*$_3$), 1.54 – 1.66 (4 H, m, 2 x C*H*$_2$), 2.63 (1 H, dt, *J* = 14.4, 7.2 Hz, C*H*$_2$), 2.79 – 2.86 (2 H, m, 2 x C*H*$_2$), 3.20 – 3.28 (1 H, m, C*H*$_2$), 3.41 – 3.49 (1 H, m, C*H*$_2$), 3.80 (1 H, d, *J* = 17.2 Hz, C*H*$_2$), 3.85 – 3.98 (3 H, m, 3 x C*H*$_2$), 4.02 – 4.08 (2 H, m, C*H*$_2$ and C*H*), 5.55 (1 H, dt, *J* = 10.8, 7.6 Hz, *cis*-C*H*), 5.92 (1 H, dt, *J* = 10.8, 8.4 Hz, *cis*-C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (CH_3), 11.4 (CH_3), 20.1 (CH_2), 20.6 (CH_2), 25.9 (CH_2), 29.7 (CH_2), 46.3 (CH_2), 48.1 (CH_2), 50.0 (CH_2), 60.0 (CH), 127.3 (CH), 130.5 (CH), 164.1 (C), 165.7 (C); *m/z* (ESI) 333.0997 [$(M+H)^+$, ^{81}Br, 98%], 331.1018 [$(M+H)^+$, ^{79}Br, 100]. Sodium hydride (60% in mineral oil, 167 mg, 4.2 mmol, 1.2 eq.) and anhydrous tetrahydrofuran (40 mL) were added to a flame-dried round-bottomed flask. Under an argon atmosphere, at 0 °C, thiophenol (0.39 mL, 3.8 mmol, 1.1 eq.) was added slowly and the reaction mixture was stirred at RT for 1 h. A solution of *cis*-3-(4-bromobut-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione (1.15 g, 3.5 mmol) in anhydrous tetrahydrofuran (40 mL) was added dropwise and the reaction mixture was stirred at RT overnight. The reaction mixture was quenched with water (a few drops) and the crude mixture was concentrated *in vacuo*. The crude mixture was diluted with water (30 mL) and extracted with ethyl acetate (4 x 30 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0 - 50% ethyl acetate in hexane) to give *cis-3-(4-(phenylthio)but-2-en-1-yl)-1,4-dipropylpiperazine-2,5-dione* ***13*** (1.12 g, 90%) as a pale yellow oil [Found: (HRMS-NSI) 361.1945. $C_{20}H_{29}N_2O_2S^+$ $(M+H)^+$ requires 361.1944]; ν_{max}(film) / cm^{-1} 2963, 2932, 2872, 2361, 1655, 1468, 1437, 1327, 1271, 1120, 1065, 893, 739; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 – 0.92 (6 H, m, 2 x C*H*$_3$), 1.52 – 1.60 (4 H, m, 2 x C*H*$_2$), 2.42 (1 H, dt, *J* = 14.4, 8.0 Hz, C*H*$_2$), 2.59 – 2.62 (1 H, m, C*H*$_2$), 2.73 – 2.76 (1 H, m, C*H*$_2$), 3.18 – 3.21 (1 H, m, C*H*$_2$), 3.41 – 3.56 (3 H, m, 3 x C*H*$_2$), 3.75 (1 H, d, *J* = 17.2 Hz, C*H*$_2$), 3.86 – 3.89 (1 H, m, C*H*$_2$), 3.95 (1 H, t, *J* = 4.8 Hz, C*H*), 4.02 (1 H, d, *J* = 17.2 Hz, C*H*$_2$), 5.47 (1 H, dt, *J* = 10.8, 8.4 Hz, *cis*-C*H*), 5.72 (1 H, dt, *J* = 10.8, 8.0 Hz, *cis*-C*H*), 7.23 (1 H, t, *J* = 7.2 Hz, Ar*H*), 7.26 – 7.30 (2 H, m, Ar*H*), 7.35 (2 H, d, *J* = 7.2 Hz, Ar*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (CH_3), 11.4 (CH_3), 20.1 (CH_2), 20.6 (CH_2), 29.8 (CH_2), 31.5 (CH_2), 46.3 (CH_2), 48.0 (CH_2), 50.0 (CH_2), 60.2 (CH), 125.3 (CH), 126.9 (CH), 129.1 (CH), 130.1 (CH), 130.9 (CH), 135.7 (C), 164.2 (C), 165.9 (C); HSQC ^{1}H/^{13}C δ (0.88 –0.92)/11.3, (0.88–0.92)/11.4, (1.52–1.60)/20.1, (1.52–1.60)/20.6, 2.42/29.8, (2.59–2.62)/29.8, (2.73–2.76)/46.3, (3.18–3.21)/48.0, (3.41–3.56)/31.5, (3.41–3.56)/31.5, (3.41–3.56)/48.0, 3.75/50.0, (3.86–3.89)/46.3, 3.95/60.2, 4.02/50.0, 5.47/125.3, 5.72/130.1, 7.23/126.9, (7.26–7.30)/129.1, 7.35/130.9.

Synthesis of *cis*-4-methoxybut-2-en-1-ol 32.[30] Sodium hydride (60% in mineral oil, 1.0 g, 25 mmol, 1.0 eq.) and anhydrous tetrahydrofuran (20 mL) were added to a flame-dried round-bottomed flask. Under an argon atmosphere, at 0 °C, *cis*-2-butene-1,4-diol **30** (6.2 mL, 75 mmol, 3 eq.) was added slowly and the reaction mixture was stirred at 0 °C for 15 min, then at RT for 1 h. Methyl iodide (1.6 mL, 25 mmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred at RT overnight and then quenched with saturated aqueous ammonium chloride solution (100 mL) and concentrated *in vacuo*. The crude mixture was diluted with saturated aqueous ammonium chloride solution (20 mL) extracted with ethyl acetate (4 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0–100% ethyl acetate in hexane) to give *cis*-4-methoxybut-2-en-1-ol **32**[30] (2.20 g, 86%) as a yellow oil [Found: (GCMS-EI) $C_5H_9O_2^-$ $(M-H)^-$ 100.7]; ν_{max}(film) / cm^{-1} 3364, 2873, 2817, 1450, 1411, 1190, 1084, 1024, 985, 948; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.90 (1 H, t, *J* = 6.0 Hz, O*H*), 3.35 (3 H, s, C*H*$_3$), 4.01 (2 H, d, *J* = 6.0 Hz, C*H*$_2$), 4.21 (2 H, t, *J* = 6.0 Hz, C*H*$_2$), 5.70 (1 H, dtt, *J* = 11.2, 6.4, 1.2 Hz, *cis*-C*H*), 5.83 (1 H, dtt, *J* = 11.2, 6.4, 1.2 Hz, *cis*-C*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 58.3 (CH_3), 59.0 (CH_2), 68.3 (CH_2), 128.5 (CH), 132.4 (CH).

Synthesis of *cis*-1-bromo-4-methoxybut-2-ene 33. *Cis*-4-methoxybut-2-en-1-ol **32** (2.0 g, 19.6 mmol) and anhydrous diethyl ether (10 mL) were added to a round-bottomed flask.

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Under an argon atmosphere, at 0 °C, PBr_3 (0.73 mL, 7.8 mmol, 0.4 eq.) was added slowly and the reaction mixture was stirred at RT overnight. The reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (4 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give *cis-1-bromo-4-methoxybut-2-ene* ***33*** (2.77 g, 86%) as an orange oil [Found: (HRMS-APCI) 162.9756. $C_5H_8BrO^-$ (M-H)$^-$ requires 162.9759]; ν_{max}(film) / cm^{-1} 2923, 2814, 1450, 1207, 1099, 959, 911, 736; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.36 (3 H, s, CH_3), 4.01 (2 H, d, *J* = 8.4 Hz, CH_2), 4.06 (2 H, d, *J* = 6.4 Hz, CH_2), 5.70 (1 H, dt, *J* = 10.8, 6.4 Hz, *cis*-C*H*), 5.89 (1 H, dtt, *J* = 10.8, 8.4, 1.6 Hz, *cis*-C*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_2), 58.5 (CH_3), 67.6 (CH_2), 128.5 (CH), 131.3 (CH); *m/z* (APCI) 164.9741 [(M-H)$^-$, ^{81}Br, 100%], 162.9756 [(M-H)$^-$, ^{79}Br, 87].

Synthesis of *cis*-(4-methoxybut-2-en-1-yl)(phenyl)sulfane 34. Sodium hydride (60% in mineral oil, 728 mg, 18.2 mmol, 1.2 eq.) and anhydrous tetrahydrofuran (20 mL) were added to a flame-dried round-bottomed flask. Under an argon atmosphere, at 0 °C, thiophenol (1.87 mL, 18.2 mmol, 1.2 eq.) was added slowly and the reaction mixture was stirred at RT for 1 h. A solution of *cis-1-bromo-4-methoxybut-2-ene* ***33*** (1.15 g, 3.5 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise and the reaction mixture was stirred at RT overnight. The reaction mixture was quenched with water (a few drops) and the crude mixture was concentrated *in vacuo*. The crude mixture was diluted with water (30 mL) and extracted with ethyl acetate (4 x 30 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0 - 5% ethyl acetate in hexane) to give *cis-(4-methoxybut-2-en-1-yl)(phenyl)sulfane* ***34*** (682.5 g, 23%) as a pale yellow oil [Found: (HRMS-APCI) 193.0687. $C_{11}H_{13}OS^-$ (M-H)$^-$ requires 193.0693]; ν_{max}(film) / cm^{-1} 2920, 2812, 1582, 1480, 1439, 1192, 1103, 1026, 738, 692; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.26 (3 H, s, CH_3), 3.58 (2 H, d, *J* = 7.2 Hz, CH_2), 3.85 (2 H, d, *J* = 6.4 Hz, CH_2), 5.60 – 5.74 (2 H, m, 2 x *cis*-C*H*), 7.19 – 7.23 (1 H, m, Ar*H*), 7.26 – 7.31 (2 H, m, Ar*H*), 7.36 – 7.39 (2 H, m, Ar*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.9 (CH_2), 58.2 (CH_3), 68.8 (CH_2), 126.8 (CH), 128.2 (CH), 129.0 (2 x CH), 129.5 (CH), 130.8 (2 x CH), 135.8 (C).

Reactions of *cis*-(4-methoxybut-2-en-1-yl)(phenyl)sulfane 34 (Table 1).

Table 1, entry 1. *Cis*-(4-methoxybut-2-en-1-yl)(phenyl)sulfane **34** (97 mg, 0.5 mmol) was added to an oven-dried pressure tube. In the glove box, KO^{t}Bu (56 mg, 0.5 mmol, 1.0 eq.) and anhydrous benzene (5 mL) were added and the reaction mixture was stirred at 130 °C for 3 h in the dark. The reaction mixture was cooled to RT, quenched with aqueous hydrochloric acid (1 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Analysis of the ^{1}H-NMR spectrum did not identify diphenyl disulfide. (Other products formed in the reaction, but could not be identified).

Table 1, entry 2. *Cis*-(4-methoxybut-2-en-1-yl)(phenyl)sulfane **34** (97 mg, 0.5 mmol) and 1,4-dipropylpiperazine-2,5-dione **7** (99 mg, 0.5 mmol, 1.0 eq.) were added to an oven-dried pressure tube. In the glove box, KO^{t}Bu (112 mg, 1.0 mmol, 2.0 eq.) and anhydrous benzene (5 mL) were added and the reaction mixture was stirred at 130 °C for 3 h in the dark. The reaction mixture was cooled to RT, quenched with aqueous hydrochloric acid (1 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The yield of diphenyl disulfide **24**[31] (6%) was determined by adding 1,3,5-trimethoxybenzene to the crude mixture as an internal standard for ^{1}H-NMR. The product was identified by the following characteristic signals; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48–7.50 (4 H, m) for diphenyl disulfide **24**. These signals are consistent with the literature values and reference samples. The compounds were all confirmed by GCMS trace, TLC and overlaying the NMR peaks to see if all the three data sets match with reference values.

Table 1, entry 3. *Cis*-(4-methoxybut-2-en-1-yl)(phenyl)sulfane **34** (97 mg, 0.5 mmol) and pinacolone **35** (0.04 mL, 0.5 mmol, 1.0 eq.) were added to an oven-dried pressure tube. In the glove box, KO^{t}Bu (112 mg, 1.0 mmol, 2.0 eq.) and anhydrous benzene (5 mL) were added and the reaction mixture was stirred at 130 °C for 3 h in the dark. The reaction mixture was cooled to RT, quenched with aqueous hydrochloric acid (1 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The yield of diphenyl disulfide **24**[31] (4%) was determined by adding 1,3,5-trimethoxybenzene to the crude mixture as an internal standard for ^{1}H-NMR. The product was identified by the following characteristic signals; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.50 (4 H, m) for diphenyl disulfide **24**. These signals are consistent with the literature values and reference samples. (Other products formed in the reaction but could not be identified).

Reduction of iodo-*m*-xylene 36 (Table 2).

Table 2, entry 1. Iodo-*m*-xylene **36** (0.07 mL, 0.5 mmol) was added to an oven-dried pressure tube. In the glove box, KO^{t}Bu (112 mg, 1.0 mmol, 2.0 eq.) and anhydrous benzene (5 mL) were added and the reaction was stirred at 130 °C for 18 h in the dark. The reaction mixture was cooled to RT, quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give iodo-*m*-xylene **36** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.48 (6 H, s, 2 x CH_3), 7.05 (2 H, d, *J* = 8.0 Hz, Ar*H*), 7.13 (1 H, t, *J* = 8.0 Hz, Ar*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.9 (2 x CH_3), 108.6 (C), 127.1 (2 x CH), 127.7 (CH), 142.2 (C). (The yield of iodo-*m*-xylene **36** (98%) was determined by adding 1,3,5-trimethoxybenzene to the crude mixture as an internal standard for ^{1}H-NMR.) These signals are consistent a commercial sample.

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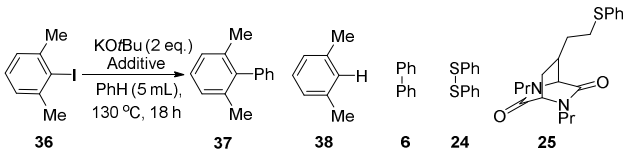
Table 2, entry 2. Iodo-*m*-xylene **36** (0.07 mL, 0.5 mmol) and 1,4-dipropylpiperazine-2,5-dione **7** (194 mg, 0.1 mmol, 0.2 eq.) were added to an oven-dried pressure tube. In the glove box, KO^{t}Bu (112 mg, 1.0 mmol, 2.0 eq.) and anhydrous benzene (5 mL) were added and the reaction was stirred at 130 ^{o}C for 18 h in the dark. The reaction mixture was cooled to RT, quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The yields of iodo-*m*-xylene **36** (16%), 2,6-dimethylbiphenyl **37**[33] (6%), xylene **38**[34] (3%) and biphenyl **6**[35] (26%) were determined by adding 1,3,5-trimethoxybenzene to the crude mixture as an internal standard for ^{1}H-NMR. The products were identified by the following characteristic signals; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.48 (6 H, s), 7.05 (2 H, d, *J* = 8.0 Hz), 7.11 (1 H, t, *J* = 8.0 Hz) for iodo-*m*-xylene **36**; δ 2.03 (6 H, s), 7.14–7.20 (5 H, m), 7.40–7.49 (3 H, m) (partly obscured by biphenyl peaks) for 2,6-dimethyl-biphenyl **37**; δ 2.32 (6 H, s) for xylene **38**; δ 7.36 (2 H, t, *J* = 8.0 Hz), 7.45 (4 H, t, *J* = 8.0 Hz), 7.60 (4 H, d, *J* = 8.0 Hz) for biphenyl **6**. (GCMS-CI) 9.78 min (*m/z* 231.9) for iodo-*m*-xylene **36**; time 10.96 min (*m/z* 182.1) for 2,6-dimethylbiphenyl **37**; 10.62 min (*m/z* 154.1) for biphenyl **6**. These signals are consistent with the literature values and reference samples.

Table 2, entry 3. Iodo-*m*-xylene **36** (0.07 mL, 0.5 mmol) and *cis*-3-[4-(phenylthio)but-2-en-1-yl]-1,4-dipropylpiperazine-2,5-dione **13** (36 mg, 0.1 mmol, 0.2 eq.) were added to an oven-dried pressure tube was added. In the glove box, KO^{t}Bu (112 mg, 1.0 mmol, 2.0 eq.) and anhydrous benzene (5 mL) were added and the reaction was stirred at 130 ^{o}C for 18 h in the dark. The reaction mixture was cooled to RT, quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*.



36 37 38 6 24 25

Entry	Additive (eq.)	36 (%)	37 (%)	38 (%)	6 (%)	24 (%)	25 (%)
3	**13** (0.2)	53[a]	4[a.]	10[a.]	13[a.]	28[a,b] (27)[c]	20[a,b] (14)[c]

[a]Yield calculated using 1,3,5-trimethoxybenzene as the internal standard ^{1}H-NMR of the crude mixture. [b]Yield calculated using the DKP additive 13 as the limiting reagent. [c]Isolated yield.

The yields of iodo-*m*-xylene **36** (53%), 2,6-dimethylbiphenyl **37**[33] (4%), xylene **38**[34] (10%), biphenyl **6**[35] (13%), diphenyl disulfide **24** (28%) and 7-(2-(phenylthio)ethyl)-2,5-dipropyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione **25** (20%) were determined by adding 1,3,5-trimethoxybenzene to the crude mixture as an internal standard for ^{1}H-NMR. The products were identified by the following characteristic signals; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.48 (6 H, s), 7.05 (2 H, d, *J* = 8.0 Hz), 7.11 (1 H, t, *J* = 8.0 Hz) for iodo-*m*-xylene **36**; δ 2.03 (6 H, s), 7.14–7.20 (5 H, m), 7.40–7.49 (3 H, m) (partly obscured by biphenyl peaks) for 2,6-dimethylbiphenyl **37**; δ 2.32 (6 H, s) for xylene **38**; δ 7.36 (2 H, t, *J* = 8.0 Hz), 7.45 (4 H, t, *J* = 8.0 Hz), 7.60 (4 H, d, *J* = 8.0 Hz) for biphenyl **6**;[35] δ 7.21–7.26 (2 H, m), 7.48–7.50 (4 H, m) for diphenyl disulfide **24**; δ 0.84 (3 H, t, *J* = 7.2 Hz), 0.91 (3 H, t, *J* = 7.2 Hz), 1.38–1.74 (5 H, m), 1.75–1.84 (1 H, m), 1.88–1.96 (1 H, m), 2.85–2.95 (3 H, m), 3.87 (1 H, d, *J* = 4.0 Hz), 4.01 (1 H, s), 7.19–7.23 (1 H, m) for 7-(2-(phenylthio)ethyl)-2,5-dipropyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione **25**. These signals are consistent with the literature values and reference samples. The crude material was purified by column chromatography (0 - 100% ethyl acetate in hexane) to yield both diphenyl disulfide **24**[31] (3 mg, 27%) as white crystals m.p. 54–56 ^{o}C (lit[32]: 57 ^{o}C); [Found: (GCMS-EI) $C_{12}H_{10}S_2$ $(M)^+$ 218.0]; ν_{max}(film) / cm^{-1} 1574, 1474, 1437, 1070, 1020, 995, 733; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21–7.25 (2 H, m, Ar*H*), 7.28–7.33 (4 H, m, Ar*H*), 7.48–7.51 (4 H, m, Ar*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 127.3 (2 x CH), 127.7 (4 x CH), 129.2 (4 x CH), 137.2 (2 x C) and 7-(2-(phenylthio)ethyl)-2,5-dipropyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione **25** (4.9 mg, 14%) as a brown oil [Found: (HRMS-EI) 360.1870. $C_{20}H_{28}N_2O_2S$ $(M)^+$ requires 360.1871]; ν_{max}(film) / cm^{-1} 2961, 2926, 2872, 1668, 1456, 1429 1290, 1258, 1120, 1070, 1024, 739; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (3 H, t, *J* = 7.2 Hz, C*H*$_3$), 0.91 (3 H, t, *J* = 7.2 Hz, C*H*$_3$), 1.38 – 1.46 (1 H, m, C*H*$_2$), 1.47–1.63 (4 H, m, C*H*$_2$), 1.64–1.72 (1 H, m, C*H*), 1.75–1.84 (1 H, m, C*H*$_2$), 1.88–1.96 (1 H, m, C*H*$_2$), 1.99–2.10 (1 H, m, C*H*$_2$), 2.85–2.95 (3 H, m, 2 x C*H*$_2$ and C*H*$_2$), 3.16–3.20 (1 H, m, C*H*$_2$), 3.46–3.54 (2 H, m, C*H*$_2$), 3.87 (1 H, d, *J* = 4.0 Hz, C*H*), 4.01 (1 H, s, C*H*), 7.19–7.23 (1 H, m, Ar*H*), 7.28–7.36 (4 H, m, Ar*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.2 (CH_3), 11.4 (CH_3), 21.0 (CH_2), 21.6 (CH_2), 25.2 (CH_2), 27.4 (CH_2), 37.2 (CH_2), 37.7 (CH), 46.4 (CH_2), 47.1 (CH_2), 59.9 (CH), 62.6 (CH), 126.7 (CH), 129.3 (2 x CH), 129.7 (2 x CH), 135.4 (C), 167.3 (C), 170.4 (C); HSQC (^{1}H/^{13}C) δ 0.84/11.2, 0.91/11.4, (1.38–1.46)/27.4, (1.47–1.63)21.0, (1.47–1.63)/21.6, (1.64–1.72)/37.7, (1.75–1.84)/25.2, (1.88–1.96)/27.4, (1.99–2.10)/25.2, (2.85–2.95)/37.2, (2.85–2.95)/46.4, (3.16–3.20)/47.1, (3.46–3.54)/46.4, (3.46–3.54)/47.1, 3.87/59.9, 4.01/62.6, (7.19–7.23)/126.7, (7.28–7.36)/129.3, (7.28 – 7.36)/129.7. (*The yields of **24** and **25** were determined based on 0.1 mmol of DKP as the limiting reagent*).

Conflicts of interest

There are no conflicts to declare.

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27. When **34** receives an electron, C-S bond cleavage to occur to form thiophenate anion and a carbon radical might be expected Seeing PhSSPh as a product might imply either (a) that the radical anion of **34** undergoes fragmentation to methoxide anion, butadiene and phenylthiyl radical, or more likely, that slow addition of a carbon radical to the allyl sulfide of **34** occurs, leading to the expulsion of phenylthiyl radical ; this radical can then dimerise to form PhSSPh. Since **13** might behave in a similar way, a blank experiment was conducted with KO*t*Bu at 130 °C; this afforded diphenyl disulfide in minute amounts (2%).
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Evidence of single electron transfer from the enolate anion of an *N,N'*-dialkyldiketopiperazine additive in BHAS coupling reactions

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TOC Entry