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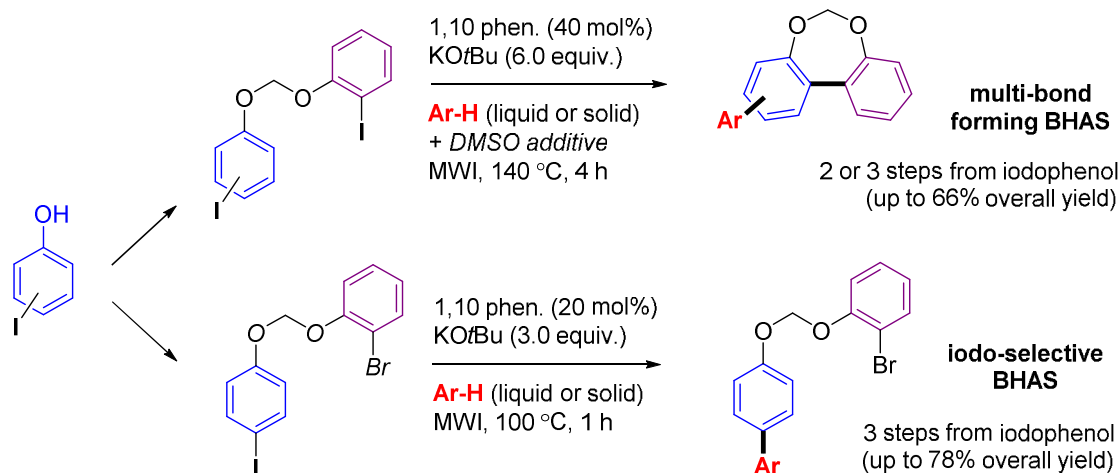
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## Multi-Bond Forming and Iodo-Selective Base-Promoted Homolytic Aromatic Substitution

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Base-promoted homolytic aromatic substitution (BHAS) has been applied as a means to effect multi-bond forming reactions. Using the dioxepine framework to illustrate the concept, BHAS was used to rapidly access regio-defined polycycles in merely 2 or 3 steps from iodophenol. Both liquid and solid arenes of an electronically-diverse nature were used as the coupling partner/solvent. DMSO additive was found to promote this multi-BHAS reaction. A pathway consistent with observations is suggested, this hypothesis was exploited to further develop an iodo-selective BHAS reaction.

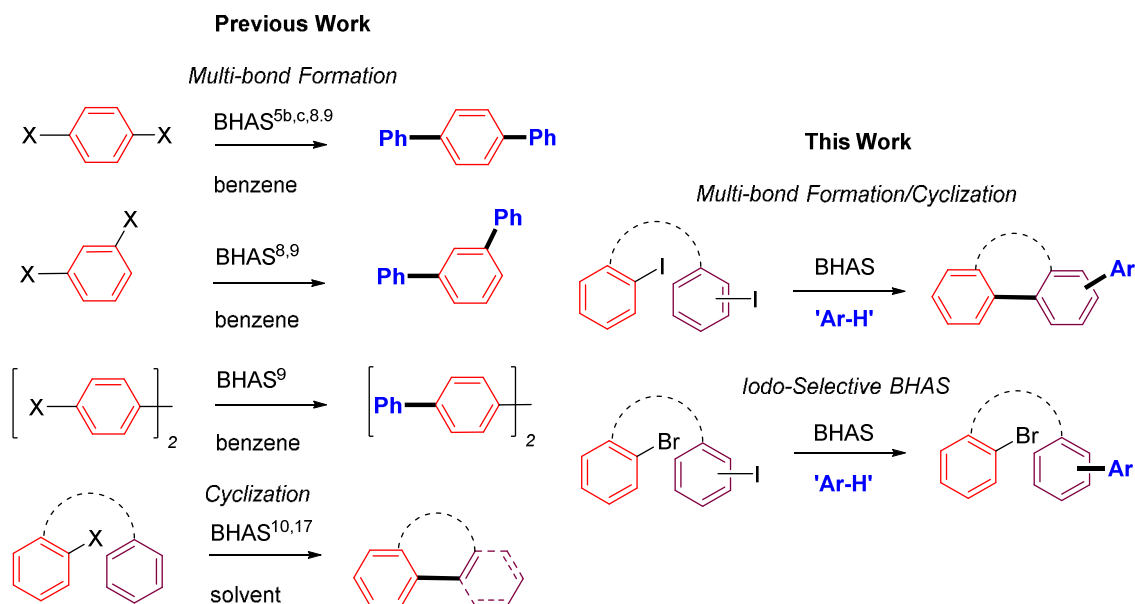
### Introduction

Since Ullmann's copper-mediated biaryl synthesis, this most crucial<sup>1</sup> of carbon-carbon bonds has been the subject of extensive synthetic advances. As a result, most methods which have been developed for the construction of multiple biaryl bonds in a single operation have hitherto relied on transition metal-catalysis. Arguably the most promising metal-free

alternative<sup>2</sup> to established transition metal-mediated methods of cross-catalysis<sup>3</sup> and C–H functionalization<sup>4</sup> is the recently-discovered Base-promoted Homolytic Aromatic Substitution (BHAS). BHAS features the use of a *tert*-butoxide base<sup>5</sup> alongside a sub-stoichiometric amount of diamine (or other) initiator to generate aryl radical species<sup>6a</sup> and is a hot topic in the contemporary iteration of a ‘radical renaissance’.<sup>6b</sup>

Multi-bond forming reactions<sup>7</sup> provide expedient, selective and often high-yielding access to desirable targets and synthetic intermediates with minimal expenditure of chemical resources. Early BHAS work has demonstrated its potential to generate multiple C–C bond formations *via* twofold substitutions<sup>5b,c,8,9</sup> and showcased interesting cyclizations.<sup>10</sup> Initial multi-BHAS examples have been restricted to substitution of two halide functional handles upon a single arene core with benzene as coupling partner (Scheme 1); further advances appear not to have been made on this aspect of BHAS methodology to date. In this work, a multi-bond forming methodology has been developed to effect both an intramolecular BHAS to a tethered arene and an intermolecular BHAS with the arene solvent/reactant. Uniquely for *multi-bond forming BHAS reactions*: i) the two reactive halo-functionalities of the multi-bond forming reaction are located on separate arenes; ii) the H–arene is not limited to benzene; and iii) conditions have been found for effective control of iodo-(over bromo-)arene selectivity. Mechanistic reasoning suggests that this reaction may comprise elements of each ‘domino’ and ‘multi-bond forming transformation of independent’ reactions.<sup>7d</sup>

## SCHEME 1. Existing and new classes of BHAS transformation



Break-through publication on transition metal-free, alkali-metal *tert*-butoxide-promoted C–H substitution have been contributed by Itami and co-workers<sup>5a</sup> and the groups of Hayashi and Shirakawa,<sup>5b</sup> Lei and Kwong,<sup>5c</sup> and Shi.<sup>5d</sup> The literature has since seen a rapidly-increasing interest in BHAS, which has demonstrated that it may be promoted photolytically<sup>9</sup> or with a variety of additives<sup>11</sup> to effect cyclization,<sup>10</sup> arene-arene coupling,<sup>12</sup> and Heck-like substitution.<sup>13</sup> Studer and Curran described<sup>6a</sup> the mechanism of this homolytic aromatic substitution as a radical chain-reaction, where the electron is passed from reactant to reactant<sup>14</sup> –*i.e.* the ‘electron is a catalyst’.<sup>6c</sup> The source of the initial electron (the initiation step) in this reaction is the subject of some debate –several suggestions have been made.<sup>15</sup>

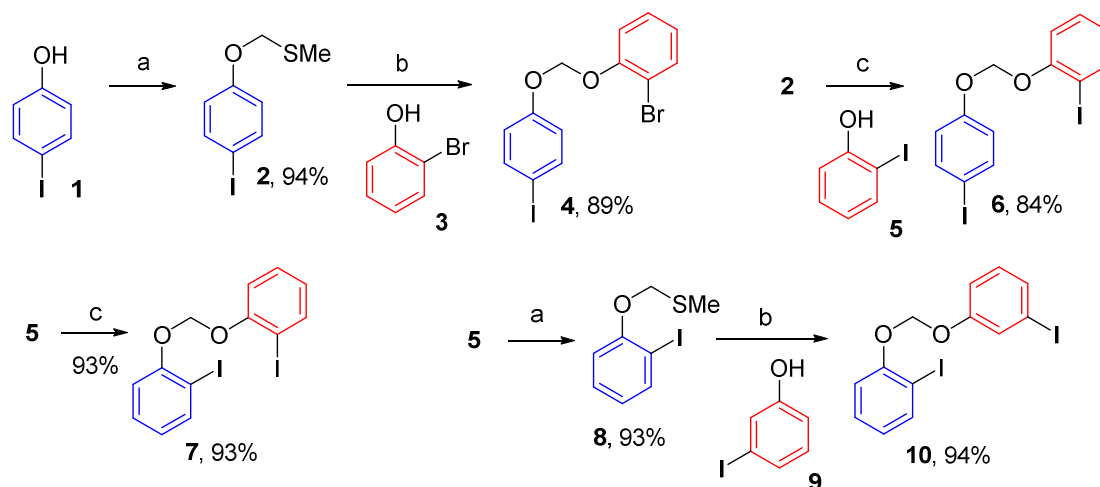
Inspired by both the ‘lactone method’<sup>16</sup> and the innovative early BHAS cyclization work of Charette and co-workers,<sup>10a</sup> the ‘acetal method’ is a strategy for the synthesis of 2,2'-(*ortho,ortho*-)biphenols via dibenzo[1,3]dioxepines utilizing BHAS for the key ring-closing reaction.<sup>17</sup> Expanding on this initial work, non-symmetrical aryl-substituted

dibenzo[1,3]dioxepines were chosen as targets to explore BHAS in the context of multi-bond forming reactions.

## Results

Synthesis of non-symmetrical and symmetrical di(haloaryloxy)methylene ethers by the previously-reported method<sup>17b</sup> saw conversion of 4-iodophenol to the mixed *O,S*-methylene diether, **2** (Scheme 2), which was substituted in a two-stage one-pot reaction with sulfuryl chloride and then 2-bromophenol, delivering bromoaryl-iodoarene **4** in 84% yield (over 2 steps). This sequence with 2-iodophenol led to 2,4'-diiodoaryloxy ether **6** (79% over 2 steps). 2-Iodophenol was also converted to 2,3'-diiodoaryloxy methane **10** (by way of **8**, 87%, two steps) and to bis-(2-iodoaryloxy)methane **7** (93%, one step).

### SCHEME 2. Dihaloarene Substrates for Multi-bond Forming BHAS

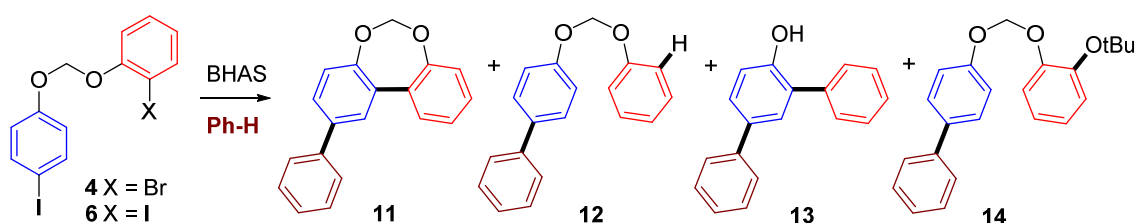


Conditions: (a) NaH, then  $\text{ClCH}_2\text{SCH}_3$ , DMF, r.t.; (b/i)  $\text{SO}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., (ii) Halophenol, NaH, DMF, r.t., then mixture from (b/i) in DMF; (c) NaH,  $\text{CH}_2\text{I}_2$ , DMF, r.t.

The cascade reaction was explored utilizing 2-bromophenoxy-4'-iodophenoxy methane, **4**, with the conditions optimised by Charette<sup>18</sup> and previously successful for the simple cyclization to dioxepines: Potassium *tert*-butoxide (6.0 equiv., *i.e.* 3.0 equivalents per halogen moiety), 1,10-phenanthroline (80 %) at 140 °C with benzene and pyridine as substrate and solvent, respectively (ratio = 1:7, entry 1, Table 1). These initial conditions

proved to be unsatisfactory, as only traces of desired product **11** were observed. Using benzene as both solvent/reactant delivered the multi-BHAS compound in 23% yield, albeit as part of a complex mixture of at least four identifiable products (**11–14**). These (by)products result from coupling -and 7-*ortho*-cyclization (**11**),<sup>17b</sup> -and de-halogenation (**12**),<sup>19</sup> -then 6-*ipso*-cyclization<sup>10a</sup> then C→O transposition<sup>20</sup> and elimination of formaldehyde (to **13**),<sup>17b</sup> - and aryl alkoxylation by nucleophilic or radical aromatic substitution (**14**).<sup>19</sup> Change of the substrate to diiodide **6** gave an improved ratio between the products (entry 3), but the yield of **11** remained low (21%).

**TABLE 1. Optimization of the Multi-Bond Forming BHAS**



Entry, Substrate	Solvent	Conc. (M)	DMSO (equiv.)	Time (h)	<b>11</b> (%)	<b>12</b> (%)	<b>13</b> (%)	<b>14</b> (%)
1, <b>4</b>	Pyr./PhH (7:1)	0.25	-	120	ND	24	ND	ND
2, <b>4</b>	C <sub>6</sub> H <sub>6</sub>	0.25	-	240	23	5	12	50
3, <b>6</b>	C <sub>6</sub> H <sub>6</sub>	0.125	-	120	21	12	11	30
4, <b>6</b>	C <sub>6</sub> H <sub>6</sub>	0.125	5.0	240	<b>59</b>	19	14	ND
5, <b>6*</b>	C <sub>6</sub> H <sub>6</sub>	0.125	5.0	240	ND	ND	ND	ND

Conditions: 1,10-Phen. (80 mol%), KOtBu (6.0 equiv.), **Ar-H** (20-40 equiv.), DMSO (5.0 equiv.), microwave irradiation (MWI), 140 °C. All yields are isolated. \*1,10-phenanthroline was excluded. ND = none detected.

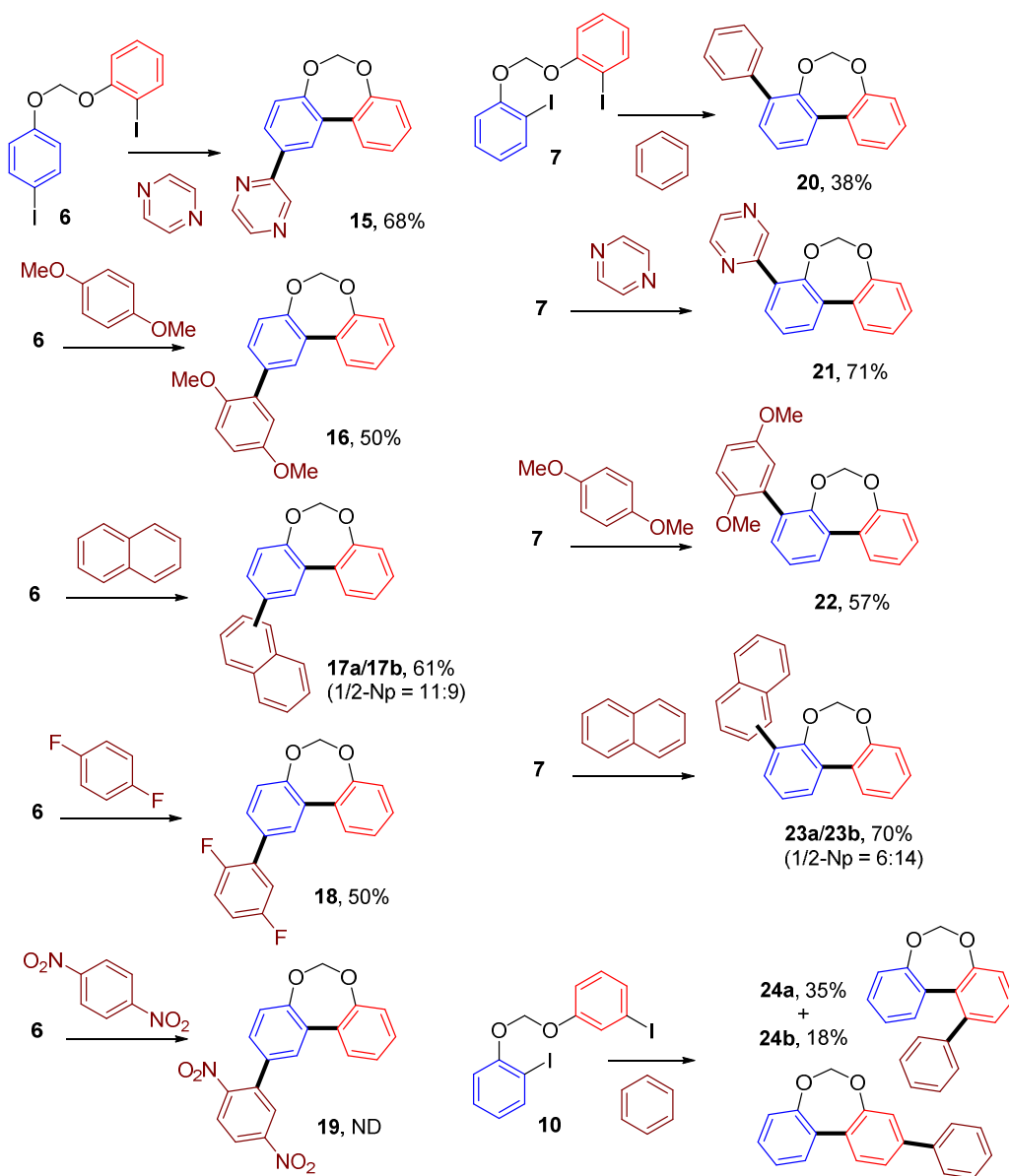
Rossi and co-workers have discovered that DMSO improves BHAS yields under photoactivation at room temperature<sup>9</sup> -happily, when a small amount of DMSO was included as an additive with the conditions above (5.0 equiv., entry 4), the outcome of this thermally-promoted reaction was also greatly improved in terms of yield and selectivity. DMSO

additive increased the isolated yield of cascade product **11** from 59%, and prevented generation of alkoxy-substituted byproduct **14**. A control experiment with DMSO in the absence of 1,10-phenanthroline showed that DMSO alone is not capable of promoting the reaction (entry 5).

With satisfactory conditions determined, the cascade BHAS was then applied to cyclization/coupling with several electronically-diverse arene partners. Complementing the usual use of liquid arenes (benzene and 1,4-difluorobenzene,) some of these were solids at room temperature (1,4-dimethoxybenzene, pyrazine, naphthalene, Scheme 3). Physical separation of the base and initiator in distinct layers of the reaction vessel prior to heating ensured that the reaction did not commence until the arene was liquefied (see Figure 1, supporting information). Diiodides **6** and **7** produced 2- and 4-aryl-substituted dioxepines **15–18** and **19–24a/b** in moderate to good yields (50–71%, Scheme 3), and *meta*-iodo substrate **10** gave a mixture of each of the two possible products (**24a/b**). Coupling of symmetrical diiodide **7** with benzene to afford **20** was notably poor in yield (38% -unsubstituted dioxepine was consistently isolated in 12–14% yield). These yields are satisfactory when considered in light of the two discrete C–C bond forming events that must take place. All 4 possible Ph-substituted isomers (**11**, **20**, **24a** and **24b**) were isolated and characterized.

Although multiple equivalents of arene are used in this method, the low cost of these coupling partners makes their use nonetheless advantageous. In contrast with typical cross-coupling substrates to form biaryls (aryl-zincs, -boronic acids, etc.), standard H-arenes not requiring preactivation or *in situ* preparation, are cheap,<sup>21</sup> non-toxic, do not require careful preparation, and are readily to hand in most chemistry laboratories.

## SCHEME 3. Multi-bond Forming to Aryl-substituted Dibenzo[1,3]dioxepines



**Conditions:** 1,10-Phen. (80 mol%), KOtBu (6.0 equiv.), Ar-H (10-30 equiv.), DMSO (5.0 equiv.), MWI, 140 °C, 4 h.

## Discussion

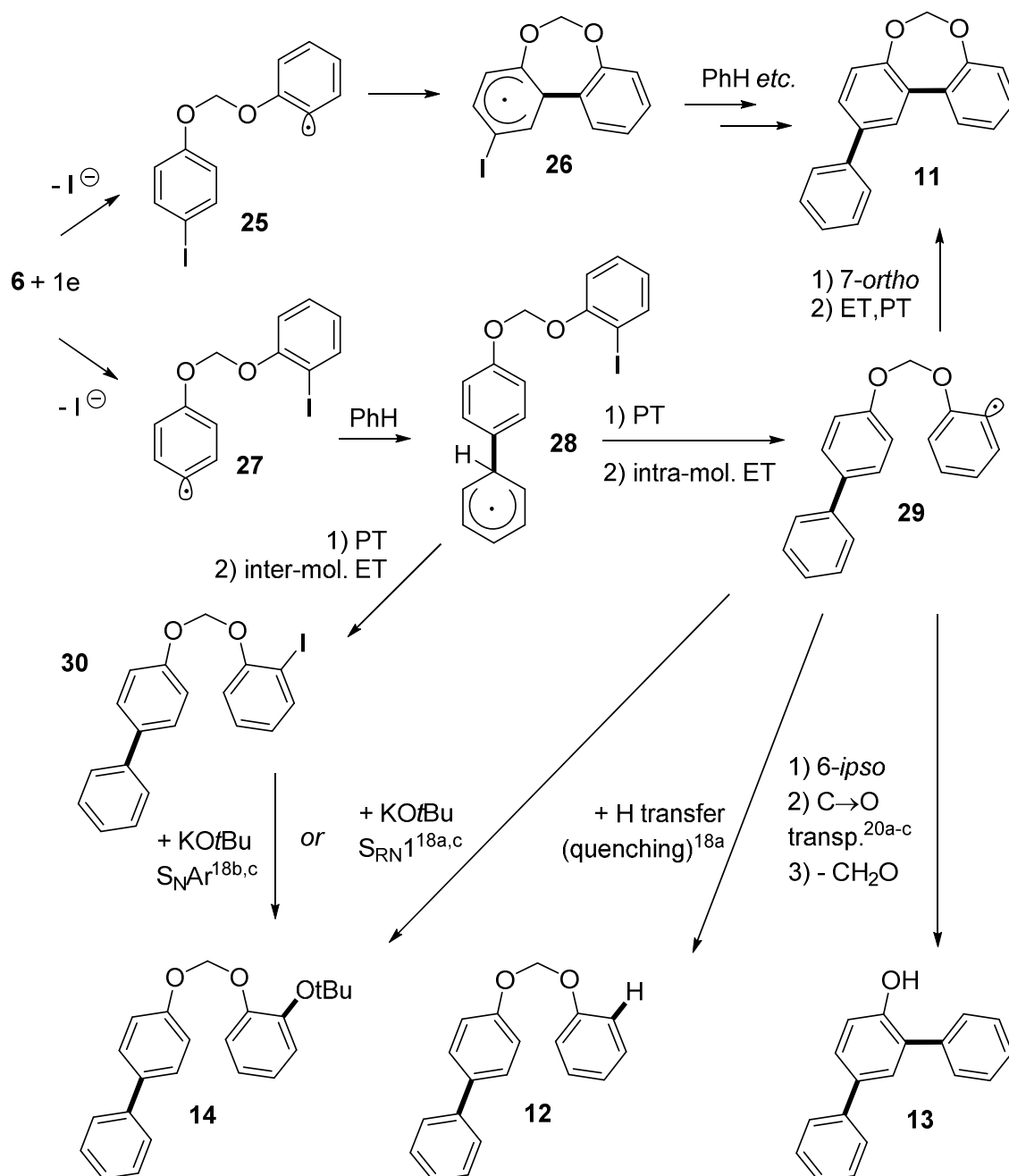
A reaction pathway accounting for observations and isolated byproducts is proposed below (Scheme 4). EPR studies have demonstrated the generation of radicals in BHAS



reactions.<sup>22a,b</sup> and a recent report by Jutand and Lei has investigated the reaction with of cyclic voltametry.<sup>22c</sup> Single-electron-transfer (SET) is thought to initially result in a radical anion located upon the haloarene –the observed non-reactivity of substrate **6** in the presence of 1,4-dinitrobenzene an established radical anion scavenger,<sup>23</sup> further supports the role of a radical anion (see Scheme 3).

The multi-BHAS from diiodoaryl **6** exhibits a uniform arene-coupling outcome at the (formerly iodo-bearing) C-(*para*) position, whereas there are a range of at least four possible modes of reaction for the C-(*ortho*) position, as evidenced by the products isolated (their distribution varies with reaction conditions, see Table 1). These results suggest that in addition to the most straightforward *ortho*- $\sigma$ -radical pathway to **11** via initially-cyclised **26**,<sup>24</sup> there is some degree of independently-operating pathway where initial substitution is at the apparently more reactive *para*-iodo-substituted position of **6** to form radical intermediate **25** then **28**. This cyclohexadienyl radical undergoes rapid transfer of its (extremely acidic) proton<sup>25,22a</sup> then either intramolecular ET (to **29** then **11**) or intermolecular ET to another iodoarenyl moiety on a different molecule (**6** or **30**), and continuation of the chain process. Intermediate *ortho*- $\sigma$ -type radical **29** can apparently follow one of four divergent pathways: Pathway 1 involves 7-*ortho* cyclization to also result in **11**, pathway 2 sees 6-*ipso* cyclization, then C $\rightarrow$ O transposition and loss of 'CH<sub>2</sub>O' to (relatively) stable phenoxy radical then phenol **13**, and in pathway 3 the *ortho*- $\sigma$ -radical abstracts hydrogen is quenched to anion with another *in situ*-generated electron-donor, giving **12**. Lastly, *tert*-butoxyl substituted **14** may be generated by either a radical<sup>19a</sup> or nucleophilic aromatic substitution<sup>11m,19b</sup> pathway, from **29** or **30**, respectively (or perhaps both).<sup>19c</sup> Having previously established that 2-bromo substrate **4** gave more of *t*-butyl ether **14** than 2-iodo **6** (see Table 1), the latter pathway appears likely. It is likely that the pathways from substrates **7** and **10** are similarly complex.

SCHEME 4. Likely Mechanism for the Multi-BHAS to form 11–14.

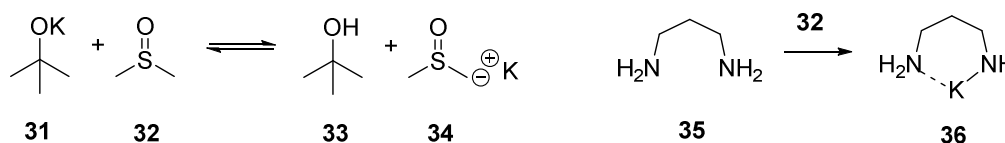


The role of DMSO co-solvent in promoting formation of **11** and suppressing the side-reactions to e.g. *tert*-butoxyl substituted arene **14** is not yet clear, but may be to enhance the domino pathway over the ‘multiple independent reaction’ pathway. Visually, these reactions

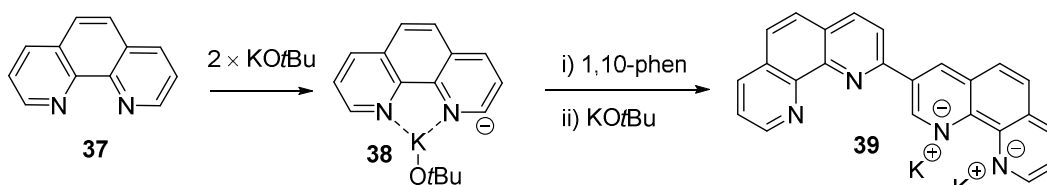
exhibited a more rapid formation of the dark coloration linked to initiation, and enhanced radical-initiation is another strong possibility.

### SCHEME 5. Possible Roles of DMSO in Promoting the BHAS Initiation

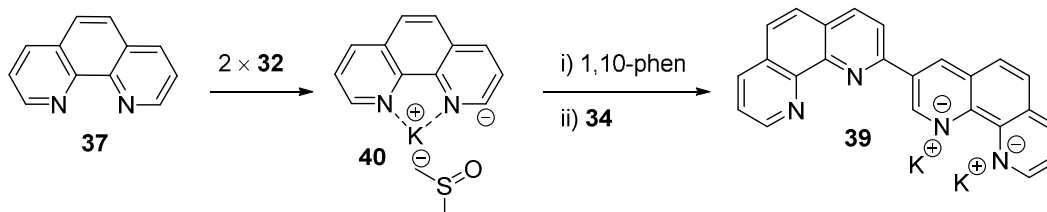
*potassium dimsyl and conversion to the stronger potassium-coordinating amide*



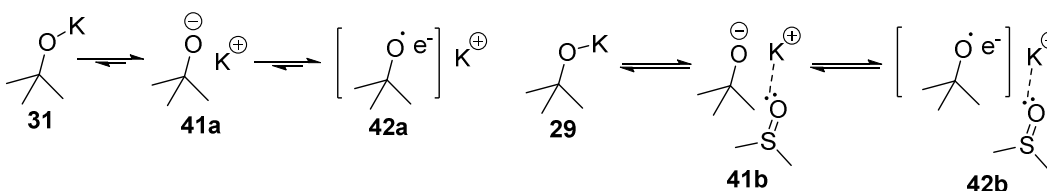
*multiple deprotonations to super electron donor (Tuttle & Murphy, 2014)*



*in the presence of potassium dimsyl*



*KOtBu equilibration to a loosely-bound electron species (Wilden, 2014), and with DMSO additive*

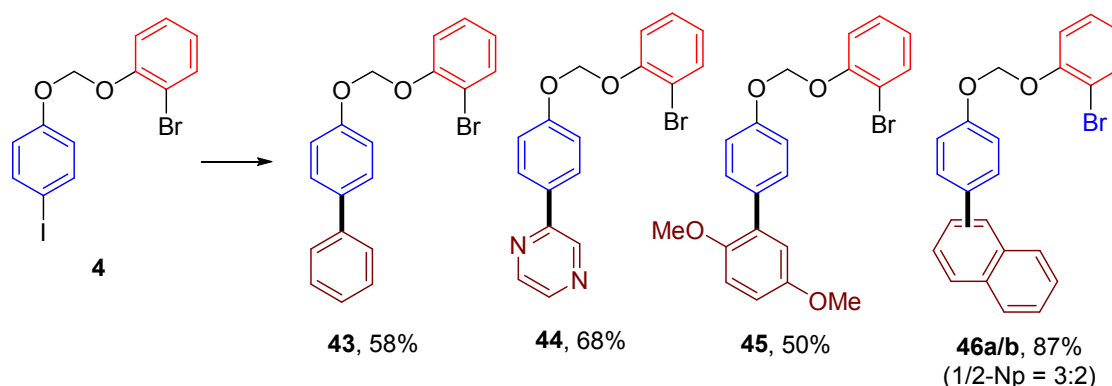


The addition of KOt-Bu to DMSO rapidly forms an equilibrium mixture with *t*-BuOH/dimsyl potassium superbases (KCH<sub>2</sub>SOCH<sub>3</sub>, **34**, Scheme 5).<sup>26</sup> In the presence of 1,10-phenanthroline, the potassium dimsyl salt may be chelating to form a potassium amide superbases **38** analogous to 1,3-diaminopropane which makes KAPA (potassium 3-aminopropyl-1-amide, **36**),<sup>27 a</sup> still more basic than potassium dimsyl by a factor of 10<sup>5</sup>–10<sup>6</sup>.<sup>27b</sup> Such a species may undergo an inner-sphere electron-transfer to form Phen<sup>•-</sup> and

$t\text{BuO}^\bullet$  in the as suggested by Lei and Jutand,<sup>22c</sup> or perhaps promote the formation of the attractive super electron donor **39**, proposed by Tuttle and Murphy, which requires deprotonations of 1,10-phenanthroline, **37**.<sup>15a</sup> To present a further possibility, Wilden and co-workers have recently described a dynamic equilibrium between ‘nearly-covalent’  $\text{KO}t\text{-Bu}$  (**29**), its charge-separated form (**39a**), and a charge separated form with a loosely-bound electron (**40a**), which alone can provide for the initial SET to the haloarene at elevated temperatures (160 °C).<sup>28</sup> It may be the case that a shifting in the equilibrium position to favor the latter of these species (**39** and **40**) is enhanced in the presence of cation-stabilising DMSO. An alternative is that the dimsyl potassium superbase, which is a strong electrolyte itself,<sup>29</sup> also has a loosely-bound electron form which can be donated. Regardless, the effect of DMSO addition is enhancement of the pathway to **11**, outcompeting that to **14**.

Given the postulated mechanism above, it was hoped that the reaction conditions could be tuned so as to block reactivity of the 2-halo position upon the initially-used bromoaryl species **4**. Selectivity for the *p*-iodo functionality BHAS was convincingly induced by excluding the DMSO additive, decreasing the reaction temperature to 100 °C, and shortening the duration of the reaction to 60 minutes, conditions which maintained the 2'-bromoaryl functionality intact (**43–46**, 50–86% yield). Chemo-/regio-selective control is so far poorly controllable in the BHAS reaction, but could allow for sequential BHAS/BHAS and BHAS/TM-catalysis coupling sequences, *e.g.* in divergent synthesis. The scope of *para*-iodo-selective coupling partners matched that of the multi-BHAS (Scheme 6).

### SCHEME 6. Iodoarene-Selective BHAS in the presence of a bromoareene moiety



**Conditions:** 1,10-Phen. (40 mol%), KO<sup>t</sup>Bu (3.0 equiv.), **Ar-H** (20-40 equiv.), MWI, 100 °C, 1 h.

### Conclusion

The BHAS reaction should be considered a synthetic option when multi-bond forming reactions are desired for rapid, modular generation of polycycles or other compounds with multiple biaryl connections. A multi-BHAS approach can work well, eschewing the use of transition-metals. Iodo-selective conditions were also established to allow attachment of only one arene to the scaffold, leaving the bromoarene intact for a host of subsequent reaction methods. The multi-bond and stepwise BHAS methods makes use of relatively cheap and environmentally benign substrates/reagents, and thus holds promise for efficient transformations in chemical Industry, decreasing costs ‘on scale’ and precluding trace amounts of toxic transition metals. Continuation of studies focusing on the further scope of the multi-bond forming BHAS and role of DMSO is currently underway in the laboratory.

### Experimental Section

#### General Experimental

Chemicals and solvents were used as commercially supplied without further purification, unless otherwise noted. Potassium *tert*-butoxide (95%), 1,10-phenanthroline (99%), sodium hydride (60% dispersion in mineral oil), dimethyl sulfoxide (Reagentplus  $\geq 99.5\%$  purity), chloromethyl methylsulfide (95%), 1,4-dimethoxybenzene (99%), pyrazine ( $\geq 99\%$ ), naphthalene (99+%), sulfuryl chloride (97%) and dimethylformamide (99.5%, anhydrous) were supplied by Aldrich. Benzene

(analytical reagent grade, obtained from Chemsupply Australia) was dried over anhydrous molecular sieves prior to use. Optimal results for this methodology required the storage of potassium *tert*-butoxide in a desiccator, and commercially-available 1,10-Phenanthroline was dried of water prior to use by addition of dry toluene azeotroping out on the rotavap (repeat x 2). Microwave reactions were performed in a *Biotage Initiator*<sup>+</sup> with a maximum power of 400 W, reactions were in new vials with securely-sealed (crimped) microwave tubes. Column chromatography was performed on Davisil (LC60A, 40-63 $\mu$ m Grace). Preparative HPLC was performed on an Agilent HPLC with a C<sub>18</sub> column (25 x 200 mm) using tetrahydrofuran and water (both HPLC grade, Merck). NMR data were recorded on a Varian Infinity-Plus 400 spectrometer (<sup>1</sup>H at 400 MHz; <sup>13</sup>C at 100 MHz), and resonances are reported in terms of chemical shift ( $\delta$ ) in parts per million (ppm) referenced to the solvent peak; coupling constants (*J*) are given in Hertz (Hz) and the number of protons per signal as *n*H. Splitting is reported as br. = broad, s = singlet, d = doublet and m = multiplet.

#### **General Procedures (1–4):**

##### **1) Multi-Bond BHAS Reactions with arenes (solids at room temperature)**

To a 2-5 mL microwave vial (Biotage) fitted with a stirring bar were added sequentially 1,10-phenanthroline (72 mg, 0.40 mmol), half the solid arene (10-20 mmol), the halo-substituted substrate (0.50 mmol), DMSO (195 mg, 2.5 mmol), the second half of the arene substrate (10–20 mmol) and lastly potassium *tert*-butoxide (336 mg, 3.0 mmol) under a shower of argon. The reagents were layered with portions of arene separating them, such that the phenanthroline and potassium *tert*-butoxide did not come into contact until such time as the arene has melted (see Figure 1 in the supporting Information). The vial was capped and the atmosphere cautiously removed by vacuum through an inserted needle with stirring, then replaced with argon (repeat three times). The reaction mixture was then heated to 140 °C via microwave irradiation for 240 minutes (reactions involving pyrazine were brought to this temperature with 10 minutes ramp time to ensure that exotherms did not occur). After this time, the blackish-coloured reaction mixture was allowed to cool to room temperature, then layered onto a plug of silica gel, which was then flushed with ethyl acetate (150

mL). The volatiles were removed by rotary evaporation under diaphragm pump vacuum (to 30 MBar), then the crude was purified by column chromatography on silica gel with mixtures of hexane and co-eluent (see specific compounds for details).

## 2) Multi-Bond BHAS Reactions with arenes (liquids at room temperature)

To a 2-5 mL microwave vial (Biotage) fitted with a stirring bar were added sequentially the 1,10-phenanthroline (72 mg, 0.40 mmol) the dihalo-substituted substrate (0.50 mmol) and potassium *tert*-butoxide (336 mg, 3.00 mmol) and anhydrous benzene (40 mmol) or 1,4-difluorobenzene (2.5 g, 22 mmol) added, followed by DMSO (195 mg, 2.50 mmol). The vial was capped and cooled 0 °C and the atmosphere cautiously removed by vacuum through an inserted needle with stirring, then replaced with argon (repeat three times). The reaction mixture was then heated to 140 °C via microwave irradiation for 240 minutes (reactions involving pyrazine were brought to this temperature with 10 minutes ramp time to ensure that exotherms did not occur). After this time, the blackish-coloured reaction mixture was allowed to cool to room temperature, then layered onto a plug of silica gel, which was then flushed with ethyl acetate (150 mL). The volatiles were removed by rotary evaporation under diaphragm pump vacuum (to 30 MBar), then the crude was purified by column chromatography on silica gel with mixtures of hexane and co-eluent (see specific compounds for details).

## 3) Iodo-Selective BHAS Reactions with arenes (solids at room temperature)

To a 2-5 mL microwave vial (Biotage) fitted with a stirring bar were added sequentially 1,10-phenanthroline (36 mg, 0.20 mmol), half the solid arene (10–20 mmol), the halo-substituted substrate (0.50 mmol), the second half of the arene substrate (10–20 mmol) and lastly potassium *tert*-butoxide (168 mg, 1.5 mmol) under a shower of argon. The reagents were layered with portions of arene separating them, such that the phenanthroline and potassium *tert*-butoxide did not come into contact until such time as the arene has melted (see labelled photograph). The vial was capped and the remainder of the procedure carried out as in **general procedure 1**, except that the reaction mixture was only heated to 100 °C for 60 minutes.

#### 4) Iodo-Selective BHAS Reactions with arenes (liquids at room temperature)

To a 2-5 mL microwave vial (Biotage) fitted with a stirring bar were added sequentially the 1,10-phenanthroline (36 mg, 0.20 mmol) the dihalo-substituted substrate (0.50 mmol) and potassium *tert*-butoxide (168 mg, 2.00 mmol) and anhydrous benzene (30 mmol) or 1,4-difluorobenzene (2.5 g, 22 mmol) added, followed by DMSO (195 mg, 2.50 mmol). The vial was capped and cooled 0 °C and the atmosphere cautiously removed by vacuum through an inserted needle with stirring, then replaced with argon (repeat three times). The remainder of the procedure carried out as in **general procedure 2**, except that the reaction mixture was only heated to 100 °C for 60 minutes.

#### Preparation of Specific Compounds

**Compound 2 / ((4-Iodophenoxy)methyl)(methyl)sulfane.** To a dried 250 mL round-bottomed flask fitted with a stirring bar and maintained under a positive pressure of argon were added 4-iodophenol (11.0 g, 50.0 mmol), DMF (50 mL) and the two stirred to -5 °C in a salt/ice bath. Sodium hydride (2.40 g, 60.0 mmol, 1.2 equiv., 60% dispersion in mineral oil) was added under argon and the reaction mixture stirred until gas evolution had ceased (~10 minutes) and then allowed to warm up to room temperature (~20 minutes), before recooling. To the opaque reaction mixture was added dropwise chloromethyl methyl sulfide (5.0 mL, 60.0 mmol, 1.2 equiv.) and the reaction mixture stirred at room temperature for 12-14 hours. After this time, the mixture was poured into H<sub>2</sub>O (300 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>/hexanes (1:1, 150 mL, × 2). The organics were washed with H<sub>2</sub>O (200 mL × 2), brine (50 mL) and dried over sodium sulfate. Filtration and removal of the volatiles by rotary evaporation under diaphragm pump vacuum (to 30 MBar) followed, then the crude was purified by column chromatography on silica gel with hexane/CH<sub>2</sub>Cl<sub>2</sub> (9:1). Isolated as a colourless semi-solid, 13.14 g, 46.9 mmol, 94% yield. **MP:** ca. room temperature; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.58 (dt, *J* = 9.0, 2.0 Hz, 2H), 6.73 (dd, *J* = 9.0, 2.3 Hz, 2H), 5.11 (s, 2H), 2.23 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 156.8, 138.3, 118.3, 84.2, 72.4, 14.6; **LRMS** (+EI, GCMS): Found 280.0; **HRMS** (+EI): Calculated [C<sub>8</sub>H<sub>9</sub>IOS]<sup>+</sup>: 279.9419; **Found**:279.9419



**Compound 4 / 1-Bromo-2-((4-iodophenoxy)methoxy)benzene. Stage 1:** Prepared in a 2-stage pseudo-1-pot reaction from **Compound 2** and 2-bromophenol by a modification of the method of Masters and Bräse (two stages, 89%).<sup>17</sup> To a stirred solution of [(4-Iodophenoxy)methyl] (methyl)sulfane **2** (1.40 g, 5.00 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) under argon in a 100 mL round-bottomed flask held at -5 °C in a salt/ice bath was added dropwise sulfonyl chloride (410 mL, 5.125 mmol, 1.025 equiv.). The ice bath was removed and the reaction mixture was stirred up to room temperature over 60 minutes, becoming pale-yellow. After this time the volatiles were removed by rotary evaporation under diaphragm pump vacuum (to 30 Mbar; this should be done with a rotary evaporator in a fume-cupboard). The crude product is invariably obtained with complete conversion and in quantitative yield, and can be checked if desired (<sup>1</sup>H-NMR, CDCl<sub>3</sub>). This crude material was taken up in dry, non-hydrolyzed or amine-free DMF and added directly to the deprotonated phenols in stage 2.

**Stage2:** To a stirred solution of 2-bromophenol (951 mg, 5.5 mmol, 1.1 equiv.) in dry, non-hydrolyzed or amine-free DMF (27.5 mL) under argon and at 0 °C was added sodium hydride (240 mg, 6.0 mmol, 1.2 equiv., 60% dispersion in mineral oil) and the mixture stirred for 30 minutes with warming to room temperature. After re-cooling to 0 °C, the aryloxymethylenechloride from stage 1 was added dropwise as a solution in DMF (5.0 mL, 2 mL washings). After stirring overnight, the reaction mixture was heated at 50 °C for 4 hours, then poured into H<sub>2</sub>O (70 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>/hexanes (1:1, 50 mL, × 2). The combined organics were washed with H<sub>2</sub>O (50 mL × 2), then brine (20 mL) and dried over sodium sulfate. Filtration and removal of the volatiles by rotary evaporation under diaphragm pump vacuum (to 30 MBar) followed, then the crude was purified by column chromatography on silica gel with hexane/CH<sub>2</sub>Cl<sub>2</sub> (9:1). Isolated as a colourless oil which solidified overnight, recrystallization from MeOH/CH<sub>2</sub>Cl<sub>2</sub> yielded the compound as colourless needles, 1.80 g, 4.45 mmol, 89% yield. **MP:** 40-42°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.63 - 7.57 (m, 2 H), 7.54 (dd, *J* = 1.6, 7.8 Hz, 1 H), 7.30 - 7.26 (m, 1 H), 7.23 - 7.16 (m, 1 H), 6.98 - 6.85 (m, 3 H), 5.74 (s, 2 H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 156.8, 153.2, 138.4, 133.6, 128.5, 124.0, 118.8,

116.7, 113.1, 91.4, 85.3; **LRMS** (+EI, GCMS): Found 403.9; **HRMS** (+EI): Calculated  $[\text{C}_{13}\text{H}_{10}\text{BrIO}_2]^+$ : 403.8903; Found: 403.8909.

**Compound 6 / 1-Iodo-2-((4-iodophenoxy)methoxy)benzene.** Prepared in a 2-stage pseudo-1-pot reaction from **compound 2** and 2-iodophenol (two steps, 84%) by a close modification of the procedure to prepare **compound 4**. Starting from ((4-Iodophenoxy) methyl)(methyl)sulfane **2** (2.45 g, 8.75 mmol), compound 6 was delivered as colourless needles, 3.98 g, 7.35 mmol, 84% yield. **MP**: 85-86°C; **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.76 (dd,  $J$  = 1.6, 7.8 Hz, 1 H), 7.66 - 7.53 (m, 2 H), 7.29 (ddd,  $J$  = 1.6, 7.2, 8.4 Hz, 1 H), 7.13 (dd,  $J$  = 1.2, 8.2 Hz, 1 H), 6.96 - 6.88 (m, 2 H), 6.78 (dt,  $J$  = 1.4, 7.5 Hz, 1 H), 5.72 (s, 2 H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>)  $\delta$  = 156.7, 155.5, 139.6, 138.4, 129.5, 124.4, 118.8, 115.2, 91.2, 87.2, 85.3; **LRMS** (+EI, GCMS): Found 451.9; **HRMS** (+EI): Calculated  $[\text{C}_{13}\text{H}_{10}\text{I}_2\text{O}_2]^+$ : 451.8765; Found: 451.8770.

**Compound 7 / Bis(2-iodophenoxy)methane.** To a stirred solution of 2-iodophenol (2.50 g, 12.3 mmol) in dimethylformamide under argon was added potassium carbonate (4.23 g, 30.6 mmol, 2.50 equiv.) then methyl iodide (0.77 mL, 1.75 g, 12.3 mmol, 2.0 eq.), and the resulting reaction mixture heated to 40 °C with stirring for 12 h. After this time, the reaction mixture was partitioned between H<sub>2</sub>O and diethyl ether (each 30 mL) and the aqueous phase extracted with diethyl ether twice more. The combined organics were washed with H<sub>2</sub>O (30 mL) once more, then with brine (5 mL) and dried over sodium sulphate. The volatiles were removed by rotary evaporation under diaphragm pump vacuum (to 30 MBar), then the crude was purified by column chromatography on silica gel with hexane and CH<sub>2</sub>Cl<sub>2</sub> (8:1). Isolated as a colourless solid, recrystallization from MeOH/CH<sub>2</sub>Cl<sub>2</sub> yielded the compound as colourless needles, 5.18 g, 93% yield. **MP**: 94-95°C; **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>)  $\delta$  = 7.79 (d,  $J$  = 7.8 Hz, 2 H), 7.39 - 7.32 (m, 2 H), 7.28 (s, 2 H), 6.81 (t,  $J$  = 7.6 Hz, 2 H), 5.82 (s, 2 H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.7, 139.6, 129.7, 124.4, 115.5, 91.7, 87.1; **LRMS** (+EI, GCMS): Found 451.9; **HRMS** (+EI): Calculated  $[\text{C}_{13}\text{H}_{10}\text{I}_2\text{O}_2]^+$ : 451.8765; Found: 451.8768.

**Compound 8 / ((2-Iodophenoxy)methyl)(methyl)sulfane.** Prepared by modification of the procedure to prepare compound 2. 2-iodophenol (5.50 g, 25.0 mmol.) was converted to **compound 9**,

isolated as a colourless liquid, 6.52 g, 23.3 mmol, 93% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.77$  (dd,  $J = 7.8, 2.0$  Hz, 1H), 7.26 - 7.34 (m, 1H), 6.88 (dd,  $J = 8.4, 1.4$  Hz, 1H), 6.75 (td,  $J = 7.5, 1.4$  Hz, 1H), 5.20 (s, 2H), 2.28 (s, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.5, 139.7, 129.2, 123.6, 114.3, 87.8, 73.3, 14.$ ; **LRMS** (+EI, GCMS): Found 280.1; **HRMS** (+EI): Calculated  $[\text{C}_8\text{H}_9\text{IOS}]^{+}$ : 279.94188; Found: 279.9422.

**Compound 10 / 1-Iodo-2-((3-iodophenoxy)methoxy)benzene.** Prepared in a 2-stage pseudo 1-pot reaction from **compound 8** and 3-iodophenol (two steps, 84%) by a close modification of the procedure to prepare compound 4. Starting from ((4-Iodophenoxy) methyl)(methyl)sulfane **9** (2.67 g, 9.5 mmol), **compound 10** was delivered as colourless needles, 4.27 g, 8.93 mmol, 94% yield. **MP**: 40 °C;  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta = 7.78$  (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.54 (d,  $J = 1.6$  Hz, 1H), 7.39 (d,  $J = 7.4$  Hz, 1H), 7.31 (td,  $J = 8.6, 2.0$  Hz, 1H), 7.10 - 7.17 (m, 2H), 7.03 (dd,  $J = 8.6, 7.4$  Hz, 1H), 6.80 (t,  $J = 7.6$  Hz, 1H), 5.74 (s, 2H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta = 157.3, 155.4, 139.7, 131.8, 130.9, 129.5, 125.8, 124.4, 115.8, 115.2, 94.2, 91.1, 87.2$ ; **LRMS** (+EI, GCMS): Found 451.9; **HRMS** (+EI): Calculated  $[\text{C}_{13}\text{H}_{10}\text{I}_2\text{O}_2]^{+}$ : 451.8765; Found: 451.8770.

**Compound 11 / 2-Phenyldibenzo[d,f][1,3]dioxepine.** Chromatography was performed with  $\text{CH}_2\text{Cl}_2$  in hexane fraction as eluent (gradient, 0 to 10%). Isolated as a colourless oil, 81.0 mg, 0.295 mmol, 59% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta = 7.85$  (d,  $J = 2.0$  Hz, 1 H), 7.73 (dd,  $J = 1.4, 7.6$  Hz, 1 H), 7.63 - 7.57 (m, 2 H), 7.51 (dd,  $J = 2.3, 8.2$  Hz, 1 H), 7.45 (t,  $J = 7.4$  Hz, 2 H), 7.38 - 7.29 (m, 2 H), 7.27 - 7.19 (m, 2 H), 7.17 (dd,  $J = 1.2, 8.2$  Hz, 1 H), 5.64 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta = 155.5, 154.6, 140.7, 137.7, 129.6, 129.2, 129.1, 128.9, 128.8, 127.7, 127.6, 127.3, 127.1, 124.7, 121.3, 121.0, 99.3$ ; **LRMS** (+EI, GCMS): Found 274.1; **HRMS** (+EI): Calculated  $[\text{C}_{19}\text{H}_{14}\text{O}_2]^{+}$ : 274.0988; Found: 274.0988.

**Compound 12 / 4-(Phenoxymethoxy)-1,1'-biphenyl.** Isolated from the test reaction to produce 2-phenyldibenzo[d,f][1,3]dioxepine (**Compound 11**) after continuation of the column with  $\text{CH}_2\text{Cl}_2$  in hexane fraction as eluent (gradient, 0 to 10%, eluted just prior to the dioxepine). Isolated as a colourless oil, 16.7 mg, 0.060 mmol, 12% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.55 - 7.50$  (m, 4 H),

7.43 - 7.38 (m, 2 H), 7.33 - 7.28 (m, 3 H), 7.19 - 7.15 (m, 2 H), 7.12 (dd,  $J = 1.0, 8.8$  Hz, 2 H), 7.03 (t,  $J = 7.2$  Hz, 1 H), 5.76 (s, 2 H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 156.9, 156.4, 140.6, 135.5, 129.6, 128.7, 128.2, 126.9, 126.8, 122.5, 116.7, 116.4, 91.1$ ; **LRMS** (+EI, GCMS): Found 276.1; **HRMS** (+EI): Calculated  $[\text{C}_{19}\text{H}_{16}\text{O}_2]^+$ : 276.1150; Found: 276.1150.

**Compound 13 / [1,1':3',1''-Terphenyl]-4'-ol.** Isolated from the test reaction to produce 2-phenyldibenzo[d,f][1,3]dioxepine (**Compound 11**) after continuation of the column with  $\text{Et}_2\text{O}$  in hexane fraction as eluent (10%). Isolated as a colourless solid, 13.0 mg, 0.054 mmol, 11% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta = 7.72$  (d,  $J = 8.2$  Hz, 2 H), 7.64 (d,  $J = 7.4$  Hz, 2 H), 7.56 (d,  $J = 7.8$  Hz, 2 H), 7.47 (t,  $J = 7.6$  Hz, 2 H), 7.41 - 7.35 (m, 1 H), 7.32 - 7.22 (m, 2 H), 7.05 - 6.97 (m, 2 H), 5.25 (s, 1 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta = 152.5, 140.7, 140.5, 136.0, 130.2, 129.5, 129.2, 128.9, 127.9, 127.7, 127.5, 127.1, 120.9, 115.9$ ; **LRMS** (+EI, GCMS): Found 246.1; **HRMS** (+EI): Calculated  $[\text{C}_{18}\text{H}_{14}\text{O}]^+$ : 246.1039; Found: 246.1045.

**Compound 14 / 4-((2-(*tert*-Butoxy)phenoxy)methoxy)-1,1'-biphenyl.** Isolated from the test reaction to produce 2-phenyldibenzo[d,f][1,3]dioxepine (**Compound 11**) after continuation of the column with  $\text{Et}_2\text{O}$  in hexane fraction as eluent (gradient, 3 to 10%). Isolated as a milky gum, 51.8 mg, 0.149 mmol, 30% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta = 7.49$ -7.65 (m, 4 H), 7.37-7.46 (m, 2 H), 7.27-7.36 (m, 1 H), 7.03-7.24 (m, 3 H), 6.87 (dq,  $J = 8.2, 1.0$  Hz, 1 H), 6.80 (t,  $J = 2.2$  Hz, 1 H), 6.70 (dq,  $J = 8.1, 0.9$  Hz, 1 H), 5.74 (m, 2 H), 1.36 ppm (m, 9 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta = 157.4, 156.6, 156.4, 140.7, 135.5, 129.5, 129.2, 128.7, 128.2, 126.9, 126.8, 118.1, 116.7, 112.5, 111.3, 91.1, 78.7, 28.8$ ; **HRMS** (+EI, GCMS): Found 348.2 (11%), 333 (8%), 292.1 (100%), 183.1 (85%); **HRMS** (+EI): Calculated  $[\text{C}_{23}\text{H}_{24}\text{O}_3]^+$ : 348.1720; Found: 348.1727

**Compound 15 / 2-(Dibenzo[d,f][1,3]dioxepin-2-yl)pyrazine.** Prepared by **general procedure 1**. Chromatography was performed with  $(\text{CH}_3)_2\text{CO}$  in hexane fraction (12.5%) as eluent. Isolated as a colourless waxy solid, 93.4 mg, 0.338 mmol, 68% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta = 9.06$  (br. s., 1 H), 8.63 (br. s., 1 H), 8.51 (br. s., 1 H), 8.39 (d,  $J = 2.0$  Hz, 1 H), 7.92 (dd,  $J = 2.2, 8.4$  Hz, 1 H), 7.82 (dd,  $J = 1.2, 7.8$  Hz, 1 H), 7.37 - 7.29 (m, 1 H), 7.29 - 7.23 (m, 2 H), 7.16 (dd,  $J = 1.4, 8.0$  Hz, 1

H), 5.64 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta$  = 156.7, 156.0, 144.1, 142.7, 141.8, 132.3, 129.2, 128.8, 128.8, 128.2, 127.9, 127.2, 124.7, 121.6, 120.9, 98.6; **LRMS** (+EI, GCMS): Found 276.1; **HRMS** (+EI): Calculated  $[\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2]^+$ : 276.0893; Found: 276.0899.

**Compound 16 / 2-(2,5-Dimethoxyphenyl)dibenzo[d,f][1,3]dioxepine.** Prepared by **general**

**procedure 1.** Chromatography was performed with  $(\text{CH}_3)_2\text{CO}$  in hexane fraction (12.5%) as eluent.

Isolated as a pale brown gum, 84.0 mg, 0.252 mmol, 50% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.81 (d,  $J$  = 2.0 Hz, 1 H), 7.69 (dd,  $J$  = 7.8, 1.2 Hz, 1 H), 7.46 (dd,  $J$  = 8.2, 2.3 Hz, 1 H), 7.27 - 7.32 (m, 1 H), 7.11 - 7.23 (m, 3 H), 6.90 - 6.95 (m, 2 H), 6.83 - 6.87 (m, 1 H), 5.63 (s, 2 H), 3.80 (s, 3 H), 3.76 ppm (s, 3 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta$  = 155.5, 154.3, 153.7, 150.7, 134.5, 130.9, 130.6, 130.6, 130.0, 129.9, 128.8, 128.8, 128.3, 124.4, 120.8, 120.4, 116.6, 113.0, 112.6, 99.0, 56.3, 55.8; **LRMS** (+EI, GCMS): Found 334.2; **HRMS** (+EI): Calculated  $[\text{C}_{21}\text{H}_{18}\text{O}_4]^+$ ; 334.1205; Found: 334.1206.

**Compound 17a and Compound 17b.** Prepared by **general procedure 1.** Chromatography was performed with  $\text{CH}_2\text{Cl}_2$  in hexane fraction as eluent (gradient, 5 to 20%). The 1-naphthyl regioisomer (**17a**) was isolated as a colourless gum, 54.0 mg, 0.15 mmol, 33% yield. Later fractions were combined and subjected to chromatography with toluene in hexane fraction (gradient, 15-30%) to deliver the 2-naphthyl isomer **17b**, which was not able to be completely separated from a coupled but not cyclized compound with a mass of 326.1 (as determined by GCMS). Isolated as a colourless gum, 44.8 mg, 0.14 mmol, 28% yield.

**Compound 17a / 2-(Naphthalen-1-yl)dibenzo[d,f][1,3]dioxepine .**  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.91 (d,  $J$  = 8.2 Hz, 1 H), 7.88 (d,  $J$  = 7.0 Hz, 1 H), 7.84 (d,  $J$  = 6.7 Hz, 2 H), 7.60 (d,  $J$  = 8.2 Hz, 1 H), 7.49 - 7.52 (m, 2 H), 7.46 - 7.48 (m, 3 H), 7.42 - 7.45 (m, 2 H), 7.38 (d,  $J$  = 1.6 Hz, 1 H), 7.31 - 7.34 (m, 1 H), 7.22 - 7.25 (m, 2 H), 6.90 (d,  $J$  = 7.4 Hz, 2 H), 5.56 - 5.63 ppm (m, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.2, 154.5, 134.5, 133.8, 133.4, 132.1, 130.9, 129.1, 128.3, 128.0, 127.7, 127.4, 126.8, 126.6, 126.0, 125.8, 125.6, 125.4, 125.2, 122.6, 116.0, 115.5, 91.2 ppm; **LRMS** (+EI, GCMS): Found 324.1; **HRMS** (+EI): Calculated  $[\text{C}_{23}\text{H}_{16}\text{O}_2]^+$ : 324.1145; Found: 324.1152.

**Compound 17b / 2-(Naphthalen-2-yl)dibenzo[d,f][1,3]dioxepine.**  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.91 - 7.98 (m, 2 H), 7.89 (d,  $J$  = 8.2 Hz, 1 H), 7.81 (d,  $J$  = 2.0 Hz, 1 H), 7.67 - 7.70 (m, 1 H), 7.49 - 7.58 (m, 2 H), 7.48 (s, 1 H), 7.42 - 7.47 (m, 2 H), 7.30 - 7.34 (m, 1 H), 7.28 (d,  $J$  = 8.2 Hz, 1 H), 7.17 - 7.22 (m, 2 H), 5.71 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.6, 154.5, 139.5, 136.9, 133.8, 131.7, 130.5, 130.4, 129.0, 128.9, 128.7, 128.6, 128.3, 127.7, 127.0, 126.2, 125.9, 125.8, 125.4, 124.5, 121.0, 120.8, 99.1; **LRMS** (+EI, GCMS): Found: 324.1; **HRMS** (+EI): Calculated  $[\text{C}_{23}\text{H}_{16}\text{O}_2]^+$ : 324.1145; Found: 324.1152.

**Compound 18 / 2-(2,5-Difluorophenyl)dibenzo[d,f][1,3]dioxepine.** Prepared by **general procedure 2**. Chromatography was performed with  $(\text{CH}_3)_2\text{CO}$  in hexane fraction (12.5%) as eluent. Isolated as a colourless oil, 83.4 mg, 0.27 mmol, 54% yield. **Caution:** Product somewhat volatile from toluene.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.83 (s, 1H), 7.71 (dd,  $J$  = 7.8, 1.6 Hz, 1H), 7.47 (dt,  $J$  = 8.5, 1.8 Hz, 1H), 7.30 - 7.36 (m, 1H), 7.20 - 7.26 (m, 2H), 7.15 - 7.20 (m, 2H), 7.12 (dd,  $J$  = 9.4, 4.7 Hz, 1H), 6.97 - 7.05 (m, 1H), 5.65 (s, 2H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta$  = 155.7, 155.1, 130.9, 129.5, 129.3, 129.1, 128.7, 128.7, 124.7, 121.2, 120.9, 117.3, 117.1, 116.9, 116.6, 116.4, 115.3, 115.1, 99.0; **LRMS** (+EI, GCMS): Found 310.1; **HRMS** (+EI): Calculated  $[\text{C}_{19}\text{H}_{12}\text{F}_2\text{O}_2]^+$ : 310.0800; Found: 310.0809.

**Compound 20 / 4-Phenyldibenzo[d,f][1,3]dioxepine.** Prepared by **general procedure 2**. Chromatography was performed with  $\text{CH}_2\text{Cl}_2$  in hexane fraction as eluent (gradient, 0 to 10%). Isolated as a colourless waxy solid, 52.6 mg, 0.192 mmol, 38% yield. **MP:**  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.64 (dd,  $J$  = 1.8, 7.6 Hz, 1 H), 7.62 - 7.58 (m, 1 H), 7.58 - 7.53 (m, 2 H), 7.48 - 7.42 (m, 2 H), 7.42 - 7.38 (m, 2 H), 7.32 (s, 2 H), 7.31 - 7.26 (m, 1 H), 7.20 (dd,  $J$  = 1.2, 7.8 Hz, 1 H), 5.52 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.8, 151.5, 137.9, 134.7, 132.2, 130.9, 130.3, 129.5, 129.2, 129.1, 128.1, 128.0, 127.3, 125.0, 124.8, 121.0, 101.0; **HRMS** (+EI, GCMS): Found 274.1; **HRMS** (+EI): Calculated  $(\text{C}_{19}\text{H}_{14}\text{O}_2^+)$ : 274.0988; Found: 274.0998.

**Compound 21 / 2-(Dibenzo[d,f][1,3]dioxepin-4-yl)pyrazine.** Prepared by **general procedure 1**. Chromatography was performed with MeOH in  $\text{CH}_2\text{Cl}_2$  as eluent (gradient, 0.5 to 1.0%). Isolated as a pale-beige gum, 98 mg, 0.356 mmol, 71% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.06 (s, 1 H), 8.69

(s, 1 H), 8.53 (d,  $J = 2.3$  Hz, 1 H), 7.80 - 7.75 (m, 1 H), 7.71 (d,  $J = 7.8$  Hz, 1 H), 7.63 (d,  $J = 7.4$  Hz, 1 H), 7.44 - 7.34 (m, 3 H), 7.29 (t,  $J = 7.4$  Hz, 1 H), 7.20 (d,  $J = 7.8$  Hz, 1 H), 5.64 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ ):  $\delta = 154.0, 152.3, 151.7, 145.9, 144.2, 142.7, 132.2, 130.3, 130.3, 130.1, 129.4, 129.1, 125.3, 124.9, 121.0, 116.2, 100.9$ ; **LRMS** (+EI, GCMS): Found 276.0; **HRMS** (+EI): Calculated  $[\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2]^+$ : 276.0893; Found: 276.0900.

**Compound 22 / 4-(2,5-Dimethoxyphenyl)dibenzo[d,f][1,3]dioxepine.** Prepared by **general procedure 1**. Chromatography was performed with EtOAc in hexane fraction as eluent (gradient, 2 to 5%). A second column was required for complete isolation;  $\text{CH}_2\text{Cl}_2$  in hexane fraction (gradient, 40 to 50%). Isolated as a colourless waxy solid, 96.2 mg, 0.288 mmol, 57% yield.  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta = 7.62$  (dd,  $J = 1.8, 7.6$  Hz, 2 H), 7.34 - 7.25 (m, 2 H), 7.25 - 7.20 (m, 2 H), 7.13 (dd,  $J = 7.8, 1.2$ Hz, 1 H), 6.92 - 6.85 (m, 2 H), 6.82 (d,  $J = 2.0$  Hz, 1 H), 5.52 (s, 2 H), 3.77 (s, 3 H), 3.71 (s, 3 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ ):  $\delta = 154.0, 153.3, 152.7, 151.2, 131.5, 131.2, 130.6, 129.9, 129.2, 129.0, 128.2, 128.1, 124.5, 124.3, 120.9, 117.0, 113.5, 111.9, 100.2, 56.2, 55.7$ ; **LRMS** (+EI, GCMS): Found 334.2; **HRMS** (+EI): Calculated  $[\text{C}_{21}\text{H}_{18}\text{O}_4]^+$ ; 334.1205; Found: 334.1205.

**Compounds 23a and 23b.** Prepared by **general procedure 1**. After initial separation of two main components containing **23a** and **23b**, (Initial yield: 112 mg, 70% yield, ratio of 1-naphthyl to 2-naphthyl = 7:3, respectively). Further separated with  $\text{CH}_2\text{Cl}_2$  in hexane (gradient, 12-20%) to deliver **23a**. The earlier-eluting fraction was subjected to chromatography with toluene in hexane fraction (gradient, 15-30%) to deliver the 2-naphthyl isomer **23b**, which was not able to be completely separated from a coupled but not cyclized compound with a mass of 326 (as determined by GCMS).

**Compound 23a / 4-(Naphthalen-1-yl)dibenzo[d,f][1,3]dioxepine.** **MP:** 143-145 °C;  $^1\text{H NMR}$  (400MHz,  $\text{CDCl}_3$ ):  $\delta = 7.90$  (dd,  $J = 3.9, 8.2$  Hz, 2 H), 7.69 (ddd,  $J = 1.8, 3.7, 7.4$  Hz, 2 H), 7.63 (d,  $J = 8.6$  Hz, 1 H), 7.57 - 7.52 (m, 1 H), 7.48 (t,  $J = 7.4$  Hz, 1 H), 7.46 - 7.41 (m, 1 H), 7.39 (d,  $J = 7.8$  Hz, 1 H), 7.37 - 7.27 (m, 4 H), 7.14 (dd,  $J = 1.4, 7.6$  Hz, 1 H), 5.32 (s, 2 H);  $^{13}\text{C NMR}$  (101MHz,  $\text{CDCl}_3$ ):  $\delta = 154.0, 152.2, 136.1, 133.5, 133.4, 132.4, 131.8, 131.3, 130.9, 129.1, 129.0, 128.3, 128.1,$

127.9, 127.1, 126.2, 126.0, 125.8, 125.2, 124.8, 124.7, 121.0, 101.0. **LRMS** (+EI, GCMS): Found 324.2; **HRMS** (+EI): Calculated  $[C_{23}H_{16}O_2]^{*+}$ : 324.1145; Found: 324.1149

**Compound 23b 4-(Naphthalen-2-yl)dibenzo[d,f][1,3]dioxepine.**  $^1H$  NMR (400MHz,  $CDCl_3$ ):  $\delta$  = 8.00 (s, 1 H), 7.86 - 7.92 (m, 3 H), 7.60 - 7.71 (m, 3 H), 7.47 - 7.54 (m, 3 H), 7.34 - 7.40 (m, 2 H), 7.30 (d,  $J$  = 7.83 Hz, 1 H), 7.18 (d,  $J$  = 7.83 Hz, 1 H), 5.48 - 5.52 (m, 2 H);  $^{13}C$  NMR (101MHz,  $CDCl_3$ ):  $\delta$  = 153.8, 151.6, 135.4, 134.6, 133.3, 132.5, 132.3, 130.5, 129.2, 129.0, 128.4, 128.1, 128.1, 127.9, 127.6, 127.4, 127.1, 126.1, 126.0, 125.1, 124.8, 121.0, 100.9; **LRMS** (+EI, GCMS): Found 324.2; **HRMS** (+EI): Calculated  $[C_{23}H_{16}O_2]^{*+}$ : 324.1145; Found: 324.1149.

**Compounds 24a and 24b.** Prepared by **general procedure 1**. Chromatography was performed on silica gel with toluene in hexane fraction as eluent (gradient, 20 to 30%) delivered first **44a** then **44b**, as well as some of the 4-phenyl coupled but not cyclised side product (15%). **Caution:** Products somewhat volatile from toluene.

**Compound 24a / 1-Phenyldibenzo[d,f][1,3]dioxepine.** Isolated as a colourless oil, 47 mg, 0.172 mmol, 34% yield.  $^1H$  NMR:  $\delta$  = 7.77 (dd,  $J$  = 9.8, 8.6 Hz, 2H), 7.66 (d,  $J$  = 8.2 Hz, 2H), 7.48 (dd,  $J$  = 7.8, 5.1 Hz, 3H), 7.40 - 7.42 (m, 1H), 7.35 (td,  $J$  = 5.1, 1.6 Hz, 1H), 7.31 (d,  $J$  = 7.4 Hz, 1H), 7.26 (d,  $J$  = 7.8 Hz, 1H), 7.18 (d,  $J$  = 7.8 Hz, 1H), 5.66 (d,  $J$  = 0.8 Hz, 2H);  $^{13}C$  NMR (CHLOROFORM-d, 101MHz):  $\delta$  = 155.8, 155.7, 141.8, 139.7, 139.7, 129.6, 129.1, 128.9, 128.8, 128.6, 127.7, 124.4, 122.9, 122.9, 120.9, 119.2, 98.4; **HRMS** (+EI): **HRMS** (+EI): Calculated  $[C_{19}H_{14}O_2]^{*+}$ : 274.0988; Found: 274.0992.

**Compound 24b / 3-Phenyldibenzo[d,f][1,3]dioxepine.** Isolated as a colourless solid, 24.5 mg, 0.091 mmol, 18% yield.  $^1H$  NMR:  $\delta$  = 7.41 (t,  $J$  = 7.8 Hz, 1H), 7.31 (dd,  $J$  = 7.4, 1.2 Hz, 1H), 7.24 - 7.28 (m, 4H), 7.22 - 7.23 (m, 1H), 7.18 - 7.21 (m, 3H), 6.86 (ddd,  $J$  = 7.8, 6.3, 2.0 Hz, 1H), 6.66 - 6.69 (m, 1H), 5.64 - 5.66 (m, 2H);  $^{13}C$  NMR:  $\delta$  = 153.3, 141.9, 140.6, 131.9, 131.8, 131.0, 129.9, 128.8, 128.6, 128.2, 128.1, 127.9, 126.9, 124.2, 121.0, 120.2, 102.7; **HRMS** (+EI): Calculated  $[C_{19}H_{14}O_2]^{*+}$ : 274.0988; Found: 274.0997.



**Compound 43 / 4-((2-Bromophenoxy)methoxy)-1,1'-biphenyl.** Prepared by **general procedure 4**.

Chromatography was performed with CH<sub>2</sub>Cl<sub>2</sub> in hexane fraction as eluent (gradient, 8% to 20%).

Isolated as a colourless oil, 108 mg, 0.304 mmol, 61% yield. **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>): δ = 7.54 (d, *J* = 9.0 Hz, 5H), 7.39 - 7.44 (m, 2H), 7.29 - 7.34 (m, 1H), 7.26 - 7.28 (m, 2H), 7.20 - 7.24 (m, 2H), 6.90 - 6.95 (m, 1H), 5.81 (s, 2H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>): δ = 156.3, 153.4, 140.5, 135.6, 133.5, 128.7, 128.5, 128.2, 126.9, 126.8, 123.7, 116.7, 116.6, 113.0, 91.5; **HRMS** (+EI): Calculated [C<sub>19</sub>H<sub>15</sub>BrO<sub>2</sub>]<sup>+</sup>: 354.0250; Found: 354.0253

**Compound 44 / 2-(4-((2-Bromophenoxy)methoxy)phenyl)pyrazine.** Prepared by **general**

**procedure 3**. Chromatography was performed with acetone in hexane fraction as eluent (gradient,

12.5% to 17.5%). Isolated as an off-white amorphous solid, 124 mg, 0.347 mmol, 69% yield. **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>): δ = 8.98 (d, *J* = 0.8 Hz, 1H), 8.59 (dd, *J* = 2.3, 1.6 Hz, 1H), 8.46 (d, *J* = 2.3 Hz, 1H), 7.98 - 8.03 (m, 2H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.25–7.32 (m, 4H), 6.90–6.97 (m, 1H), 5.84 (s, 2H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>): δ = 158.4, 153.3, 152.3, 144.1, 142.4, 141.8, 133.6, 130.7, 128.5, 128.4, 124.0, 116.9, 116.8, 113.2, 91.2; **HRMS** (+EI): Calculated [C<sub>17</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: 356.0155; Found: 356.0162.

**Compound 45 / 4'-((2-Bromophenoxy)methoxy)-2,5-dimethoxy-1,1'-biphenyl.** Prepared by

**general procedure 3**. Chromatography was performed with EtOAc in hexane fraction as eluent

(gradient, 2 to 5%). A second column was required for complete isolation; CH<sub>2</sub>Cl<sub>2</sub> in hexane fraction (gradient, 25 to 50%). Isolated as a colourless solid, 105 mg, 0.253 mmol, 50% yield. **MP**: 62–64 °C; **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>): δ = 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.50–7.53 (m, 2H), 7.25–7.31 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.88–6.96 (m, 3H), 6.84 (dd, *J* = 8.6, 3.4 Hz, 1H), 5.79–5.84 (m, 2H), 5.81 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>): δ = 156.1, 153.7, 153.5, 150.7, 133.5, 132.7, 131.0, 130.7, 128.5, 123.7, 116.7, 116.6, 116.0, 113.0, 112.8, 112.5, 91.5, 56.3, 55.8; **HRMS** (+EI): Calculated [C<sub>21</sub>H<sub>19</sub>BrO<sub>4</sub>]<sup>+</sup>; 414.0461; Found: 414.0469.

**Compounds 46a and 46b.** Prepared by **general procedure 3**. Chromatography was performed on silica gel with CH<sub>2</sub>Cl<sub>2</sub> in hexane fraction as eluent (gradient, 5 to 10%), by which the 1-naphthyl and

2-naphthyl isomers were separable save a small mixed fraction between the two. The second compound was further cleaned by running on silica gel with toluene in hexane (gradient, 10 to 25%). Isolated as colourless solids, 176 mg, 0.43 mmol, 87% yield; 1-Np to 2-Np ratio = 6:4.

**Compound 46a / 1-(4-((2-Bromophenoxy)methoxy)phenyl)naphthalene.** Isolated as a colourless solid, 85 mg, 0.21 mmol, 42% yield. **MP:** 80–82 °C; **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>): δ = 7.90 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.47 - 7.54 (m, 2H), 7.39 - 7.47 (m, 4H), 7.30 - 7.36 (m, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 5.87 (s, 2H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>): δ = 156.3, 153.5, 139.6, 135.1, 133.8, 133.6, 131.7, 131.3, 128.6, 128.3, 127.5, 127.0, 126.0, 126.0, 125.8, 125.4, 123.8, 116.7, 116.3, 116.3, 113.1, 91.6; **HRMS** (+EI): Calculated [C<sub>23</sub>H<sub>17</sub>BrO<sub>2</sub>]<sup>+</sup>: 404.0406; Found: 404.0410.

**Compound 46b / 2-(4-((2-Bromophenoxy)methoxy)phenyl)naphthalene.** Isolated as a colourless solid, 69 mg, 0.172 mmol, 34% yield. **MP:** 73-75 °C; **<sup>1</sup>H NMR** (400MHz, CDCl<sub>3</sub>): δ = 7.99 (s, 1H), 7.88 (q, *J* = 8.2 Hz, 3H), 7.72 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.66 - 7.70 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.44 - 7.52 (m, 2H), 7.26 - 7.31 (m, 4H), 6.91 - 6.97 (m, 1H), 5.84 (s, 2H); **<sup>13</sup>C NMR** (101MHz, CDCl<sub>3</sub>): δ = 156.5, 137.9, 135.6, 135.6, 133.7, 133.5, 132.4, 128.6, 128.5, 128.4, 128.1, 127.6, 126.3, 125.8, 125.4, 125.3, 123.8, 116.8, 116.8, 113.1, 91.6; **HRMS** (+EI): Calculated [C<sub>23</sub>H<sub>17</sub>BrO<sub>2</sub>]<sup>+</sup>: 404.0406; Found: 404.0408.

### Acknowledgments

This work was supported by a Vice-Chancellor's Research Fellowship from the Queensland University of Technology. Mass spectra were acquired by *Ms Anithahini (Anitha) Jeyasingham* with support from *Prof. Stephen Blanksby* and QUT's Central Analytical Facility (CARF). *K.-S. M.* acknowledges valuable mentoring from *Prof. Steven Bottle* and *Prof. Stefan Bräse*.

### Electronic Supplementary Information

Full  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for 26 new compounds and a representation showing the set-up for coupling of solid at room-temperature arenes (Figure S 1) is compiled in a word document. This material is available on the internet at DOI: 10.XXXX

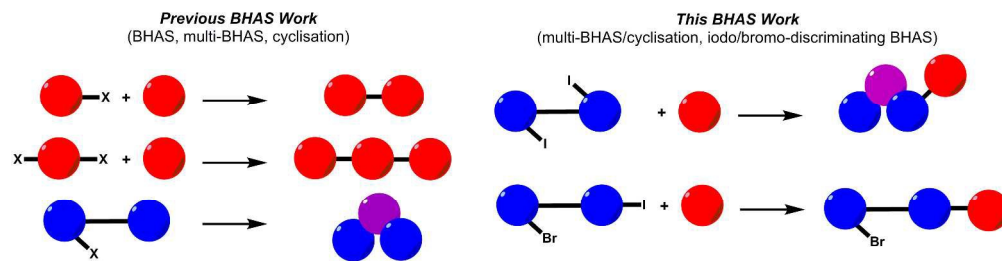
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- What's new for multi-BHAS? 1) *BHAS can be used for metal-free intra/inter-molecular coupling combinations*  
 2) *solid arenes are effective coupling partners*  
 3) *DMSO as additive enhances reactivity/selectivity*  
 4) *selective reaction of I over Br under appropriate conditions*

317x123mm (300 x 300 DPI)